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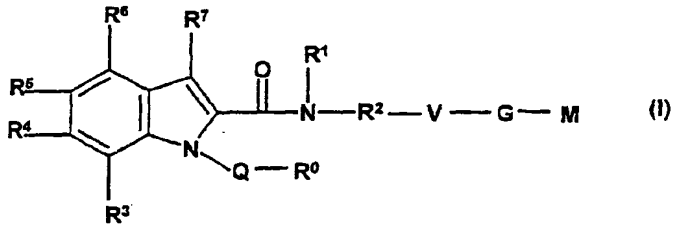
(54) Indole-2-carboxamides as factor Xa inhibitors

(57) The present invention relates to compounds of the formula I,



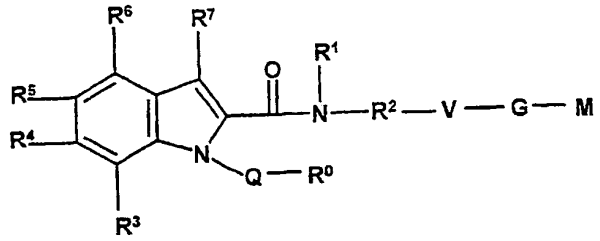
(I)

in which R^0 ; R^1 ; R^2 ; R^3 ; R^4 ; R^5 ; R^6 ; R^7 ; Q; V, G and M have the meanings indicated in the claims. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them

EP 1 314 733 A1

Description

[0001] The present invention relates to compounds of the formula I,



(I)

in which R^0 ; R^1 ; R^2; R^3 ; R^4 ; R^5; R^6; R^7; Q; V, G and M have the meanings indicated below. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

[0002] Normal haemeostasis is the result of a complex balance between the processes of clot initiation, formation and clot dissolution. The complex interactions between blood cells, specific plasma proteins and the vascular surface, maintain the fluidity of blood unless injury and blood loss occurs (EP-A-987274). Many significant disease states are related to abnormal haemeostasis. For example, local thrombus formation due to rupture of atherosclerotic plaque is a major cause of acute myocardial infarction and unstable angina. Treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous angioplasty may be accompanied by acute thrombolytic reclosure of the affected vessel.

[0003] There continues to be a need for safe and effective therapeutic anticoagulants to limit or prevent thrombus formation. It is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade like factor Xa and/or factor VIIa activity. It is now believed that inhibitors of factor Xa carry a lower bleeding risk than thrombin inhibitors (A. E. P. Adang & J. B. M. Rewinkel, Drugs of the Future 2000, 25, 369-383).

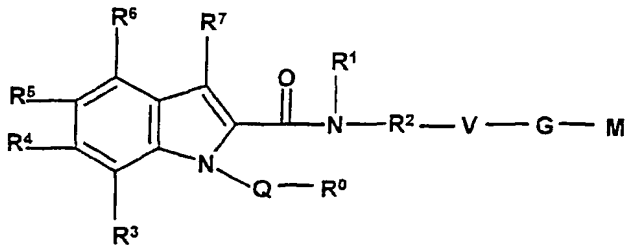
Low molecular weight, factor Xa-specific blood clotting inhibitors that are effective but do not cause unwanted side effects have been described, for example, in WO-A-95/29189. However, besides being an effective factor Xa-specific blood clotting inhibitor, it is desirable that such inhibitors also have further advantageous properties, for instance stability in plasma and liver and selectivity versus other serine proteases whose inhibition is not intended, such as thrombin. There is an ongoing need for further low molecular weight factor Xa specific blood clotting inhibitors, which are effective and have the above advantages as well.

[0004] Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800, WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty. Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition. Certain inhibitors of factor VIIa have already been described. EP-A-987274, for example discloses compounds containing a tripeptide unit which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is an ongoing need for further low molecular weight factor VIIa inhibitory blood clotting inhibitors.

WO-A-99/33800 discloses indole derivatives, which inhibit factor Xa activity.

[0005] The present invention satisfies the above needs by providing novel compounds of the formula I which exhibit better factor Xa and/or factor VIIa inhibitory activity and are favorable agents with high bioavailability.

[0006] Thus, the present invention relates to compounds of the formula I,



(I)

wherein

R^0 is
1. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R^8,
2. a monocyclic or bicyclic 5- to 14-membered heteroaryl out of the group pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, or
3. a monocyclic or bicyclic 5- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, and which is additionally substituted by a monocyclic or bicyclic 5- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

R^8 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,
6. $-NH_2$,
7. a monocyclic or bicyclic 5- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,
8. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or
9. $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

provided that R^8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^o is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; $-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, $-(C_1-C_6)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH;

R^1 is hydrogen atom or $-(C_1-C_4)$-alkyl,

R^2 is a direct bond or $-(C_1-C_4)$-alkylen, or

R^1 and R^2 together with the nitrogen atom and V to which they are bonded form a 5- to 7- membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, =O, $-(C_1-C_4)$-alkyl, $-(C_1-C_4)$-alkoxy, $-NO_2$, -C(O)-OH, -CN, $-NH_2$, $-C(O)-O-(C_1-C_4)$-alkyl, $-(C_1-C_8)$-alkylsulfonyl, $-SO_2$, $-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-N-[(C_1-C_8)-alkyl]_2$, $-NR^{10}-C(O)-NH-(C_1-C_8)$-alkyl, $-C(O)-NH_2$, $-SR^{10}$, or $-NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]_2$,

wherein R^{10} is hydrogen atom or $-(C_1-C_4)$-alkyl,

V is
1. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a monocyclic or bicyclic 5- to 14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is
a direct bond, $-(CH_2)_m-NR^{10}-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-CH(OH)-(CH_2)_n-$, $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_n-$, $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-C(O)-(CH_2)_n-$, $-(CH_2)_m-C(O)-(CH_2)_n-$, $-(CH_2)-S-(CH_2)_n-$, $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$, $-(CH_2)_m-NR^{10}-$, $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ or $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$,

n and m are
are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R^{10} is
hydrogen atom or $-(C_1-C_4)$-alkyl,

M is
1. a hydrogen atom,
2. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-C(O)-NR^{11}R^{12}$,
4. $-(CH_2)_m-NR^{10}$,
5. $-(C_6-C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. $-(C_5-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
7. (C_3-C_7)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
8. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

R^{11} and R^{12} are
independently of one another identical or different and are

1. hydrogen atom,
2. $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
3. $-(C_6-C_{14})$-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13},
4. $-(C_6-C_{14})$-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
5. $-(C_5-C_{14})$-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or
6. $-(C_5-C_{14})$-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13},

R^{11} and R^{12}
together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{13} is
halogen, $-NO_2$, -CN, -OH, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkyloxy, $-CF_3$, $-C(O)-NH_2$ or $-NH_2$, and

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are hydrogen atom, F, Cl, Br, I, (C_1-C_4)-alkyl, $-CF_3$, phenyl, phenyl-(C_1-C_4)-alkyl-, (C_1-C_4)-alkoxy, wherein alkoxy is unsubstituted or substituted one

to three times by halogen, phenyloxy-, phenyl-(C_1-C_4)-alkoxy-, -OH, -NO_2, -$NR^{11}R^{12}$, -NR^{10}-SO_2-R^{10}, -S-R^{10}, -SO_n-R^{10}, wherein n is 1 or 2, -SO_2-$NR^{11}R^{12}$, -CN or -CO-R^{10},
wherein R^{10}, R^{11} and R^{12} are as defined above

[0007] in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0008] The present invention also relates to the compounds of the formula I, wherein

R^0 is
1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,
2. a bicyclic 5- to 14-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl,
wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyridazinyl and pyrazinyl,
wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8
3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl and pyrazinyl,
wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8

R^8 is
1. halogen, such as F, Cl, Br or J,
2. -C(O)-NH_2,
3. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or
4. -O-(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R^8 is at least one halogen, -C(O)-NH_2 or -O-(C_1-C_8)-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; -SO_2- or -(C_1-C_6)-alkylen,

R^1 is hydrogen atom or -(C_1-C_2)-alkyl,

R^2 is a direct bond or -(C_1-C_2)-alkylen, or

R^1 and R^2 together with the nitrogen atom and V to which they are bonded form a 5- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine,
wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -(C_1-C_4)-alkyl or -NH_2,

V is
1. a 3- to 7-membered cyclic residue out of the group containing compounds which are derived from aziridine, azirine, azetidine, pyrrole, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine,
furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine,

1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine,
thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,
wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxalinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is — a direct bond, $-(CH_2)_m-$, or $-(CH_2)_m-NR^{10}-$,

m is — the integers zero, 1, 2, 3 or 4,

R^{10} is — hydrogen atom or $-(C_1-C_4)$-alkyl,

M is —
1. a hydrogen atom,
2. $-(C_6-C_{14})$-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. $-(C_1-C_6)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
4. (C_3-C_6)-cycloalkyl,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are hydrogen atom, F, Cl, Br, $-(C_1-C_4)$-alkyl, $-CF_3$, $-(C_1-C_4)$-alkoxy, phenyl-(C_1-C_4)-alkoxy-, $-NO_2$ or $-SO_n-R^{10}$, wherein n is 1 or 2, and R^{10} is as defined above,
in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0009] The present invention also relates to the compounds of the formula I, wherein

R^0 is —
1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^8,
2. a monocyclic 5- to 14-membered heteroaryl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heteroaryl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl,
wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R^8,

R^8 is — F, Cl, Br, methoxyl, $-C(O)-NH_2$ or $-O-CF_3$,

Q — is a direct bond, $-C(O)-$; $-SO_2-$, methylene or ethylene,

R^1 is — hydrogen atom,

R^2 is — a direct bond or methylen, or

R^1 and R^2 — together with the nitrogen atom and V to which they are bonded form a 5- to 7-membered cyclic group out of the group piperidine and piperazine,

R^{14} is — halogen, methyl, ethyl or $-NH_2$,

V is —
1. a residue out of the group containing compounds which is derived from isoquinol, quinol, quinazoline, piperidine, tetrahydropyran, piperazine and isoxazole,
wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or

	2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or
G is	a direct bond, $-(CH_2)_m-$, or $-(CH_2)_m-NR^{10}-$,
m is	the integers zero, 1 or 2,
R^{10} is	hydrogen atom or $-(C_1-C_4)$-alkyl,
M is	a hydrogen atom, (C_2-C_4)-alkyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, pyridinyl or (C_3-C_6)-cylohexyl,
R^3, R^4, R^5, R^6 and R^7 are	independent of one another are identical or different and are hydrogen atom, Cl, F, Br, methyl, ethyl, $-O-CF_3$, $-NH-C(O)-C(CH_3)_3$, methoxyl, phenyl, $-O-CH_2$-phenyl, -CN, $-NO_2$ or $-SO_2-CH_3$,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0010] The present invention also relates to the compounds of the formula I, which are
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-nitro-1 H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-nitro-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-methyl-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5,7-din itro-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5,7-difluoro-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-chloro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-bromo-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- 1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-fluoro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-chloro-th iophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide or
1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-7-methyl-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

[0011] In general, the meaning of any group, residue, heteroatom, number etc. which can occur more than once in the compounds of the formula I, is independent of the meaning of this group, residue, heteroatom, number etc. in any other occurrence. All groups, residues, heteroatoms, numbers etc. which can occur more than once in the compounds of the formula I can be identical or different.

[0012] As used herein, the term alkyl is to be understood in the broadest sense to mean hydrocarbon residues which can be linear, i. e. straight-chain, or branched and which can be acyclic or cyclic residues or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkyloxy residue, an alkyloxycarbonyl residue or an arylalkyl residue. Examples of alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl, the n-isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tBu, tert-pentyl, sec-butyl, tert-butyl or tert-pentyl.

[0013] Unsaturated alkyl residues are, for example, alkenyl residues such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl, or alkynyl residues such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl. Alkyl residues can also be unsaturated when they are substituted.

[0014] Examples of cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5 or 6 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which can also be substituted and/or unsaturated. Unsaturated cyclic

alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

[0015] Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like (C_1-C_8)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_8)-alkyl, (C_3-C_6)-cycloalkyl, and unsaturated (C_2-C_8)-alkyl like (C_2-C_8)-alkenyl or (C_2-C_8)-alkynyl. Similarly, a group like (C_1-C_4)-alkyl is to be understood as comprising, among others, saturated acyclic (C_1-C_4)-alkyl, and unsaturated (C_2-C_4)-alkyl like (C_2-C_4)-alkenyl or (C_2-C_4)-alkynyl.

[0016] Unless stated otherwise, the term alkyl preferably comprises acyclic saturated hydrocarbon residues which have from one to six carbon atoms and which can be linear or branched. A particular group of saturated acyclic alkyl residues is formed by (C_1-C_4)-alkyl residues like methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tBu.

[0017] Unless stated otherwise, and irrespective of any specific substituents bonded to alkyl groups which are indicated in the definition of the compounds of the formula I, alkyl groups can in general be unsubstituted or substituted by one or more, for example one, two or three, identical or different substituents. Any kind of substituents present in substituted alkyl residues can be present in any desired position provided that the substitution does not lead to an unstable molecule. Examples of substituted alkyl residues are alkyl residues in which one or more, for example 1, 2 or 3, hydrogen atoms are replaced with halogen atoms, in particular fluorine atoms.

[0018] The term "mono- or bicyclic 5- to 14-membered heteroaryl" refers to (C_5-C_{14})-aryl in which one or more of the 5 to 14 ring carbon atoms are replaced by heteroatoms such as nitrogen, oxygen or sulfur. Examples are pyridyl; such as 2-pyridyl, 3-pyridyl or 4-pyridyl; pyrrolyl; such as 2-pyrrolyl and 3-pyrrolyl; furyl; such as 2-furyl and 3-furyl; thienyl; such as 2-thienyl and 3-thienyl; imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl, pyrazinyl, pyrimidinyl,
indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl.

[0019] The term "R^1 and R^2 together with the nitrogen atom and V to which they are bonded form a 5- to 7-membered cyclic group" refers to structures of heterocycles which can be derived from compounds such as piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine.

[0020] The term "a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms" refers to structures of heterocycles which can be derived from compounds such as , aziridine, azirine, azetidine, pyrrole, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine,
furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine.

[0021] The term "R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 7-membered monocyclic heterocyclic ring" refers to residues which can be derived from compounds such as piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine.

[0022] The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the , the 4-15 membered mono- or polycyclic group could only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, the 4-15 membered mono- or polycyclic group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated analogues of the before-listed heterocycles from which this group may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (= morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc.

[0023] The 4-15 membered mono- or polycyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a

pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Indolyl can be indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl or indol-7-yl. Similarly benzimidazolyl, benzoxazolyl and benzothiazol residues can be bonded via the 2-position and via any of the positions 4, 5, 6, and 7. Quinolinyl can be quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl or quinolin-8-yl, isoqinolinyl can be isoquinol-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl or isoquinolin-8-yl. In addition to being bonded via any of the positions indicated for quinolinyl and isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl and 1,2,3,4-tetrahydroisoquinolinyl can also be bonded via the nitrogen atoms in 1-position and 2-position, respectively.

Unless stated otherwise, and irrespective of any specific substituents bonded to the 4-15 membered mono- or polycyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, the 4-15 membered mono- or polycyclic group can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkyloxy, in particular (C_1-C_4)-alkyloxy, (C_1-C_4)-alkylthio, halogen, nitro, amino, ((C_1-C_4)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C_1-C_4)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 4-15 membered mono- or polycyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C_1-C_4)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C_2-C_4)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S,S-dioxotetrahydro-thienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 4-15 membered mono- or polycyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

[0024] The 3-7 membered monocyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Unless stated otherwise, and irrespective of any specific substituents bonded to the 3-7 membered monocyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkyloxy, in particular (C_1-C_4)-alkyloxy, (C_1-C_4)-alkylthio, halogen, nitro, amino, ((C_1-C_4)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C_1-C_4)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 3-7 membered monocyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl- (C_1-C_4)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C_2-C_4)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C_1-C_4)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms

can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S, Sdioxotetrahydrothienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 3-7 membered monocyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

[0025] Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, particularly preferably chlorine or bromine.

[0026] Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

[0027] Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

[0028] Physiologically tolerable salts of the compounds of formula I are nontoxic salts that are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxyl group COOH, are for example alkali metal salts or alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quaternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. Basic groups contained in the compounds of the formula I, for example amino groups or guanidino groups, form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. Compounds of the formula I which simultaneously contain a basic group and an acidic group, for example a guanidino group and a carboxyl group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

[0029] Salts of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an inorganic or organic acid or base in a solvent or dispersant, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiologically tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as intermediates for carrying out further chemical modifications of the compounds of the formula I or as starting materials for the preparation of physiologically tolerable salts. The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols.

[0030] The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives, as well as active metabolites of the compounds of the formula I. The invention relates in particular to prodrugs and protected forms of the compounds of the formula I which can be converted into compounds of the formula I under physiological conditions. Suitable prodrugs for the compounds of the formula I, i. e. chemically modified derivatives of the compounds of the formula I having properties which are improved in a desired manner, for example with respect to solubility, bioavailability or duration of action, are known to those skilled in the art. More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985, , Fleisher et al., Advanced Drug Delivery Reviews 19 (1996) 115-130; or H. Bundgaard, Drugs of the Future 16 (1991) 443 which are all incorporated herein by reference. Suitable prodrugs for the compounds of the formula I are especially acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino groups and the guanidino group and also ester prodrugs and amide prodrugs of carboxylic acid groups which may be present in compounds of the formula I. In the acyl prodrugs and carbamate prodrugs one or more, for example one or two, hydrogen atoms on nitrogen atoms in such groups are replaced with an acyl group or a carbamate, preferably a (C_1-C_6)-alkyloxycarbonyl group. Suitable acyl groups and carbamate groups for acyl prodrugs and carbamate prodrugs are, for example, the groups R^{p1}-CO- and R^{p2}O-CO-, in which R^{p1} is hydrogen, (C_1-C_{18})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl-, (C_6-C_{14})-aryl, Het-, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl- or Het-(C_1-C_4)-alkyl- and in which R^{p2} has the meanings indicated for R^{p1} with the exception

of hydrogen.

[0031] Especially preferred compounds of the formula I are those wherein two or more residues are defined as indicated before for preferred compounds of the formula I, or residues can have one or some of the specific denotations of the residues given in their general definitions or in the definitions of preferred compounds before. All possible combinations of definitions given for preferred definitions and of specific denotations of residues explicitly are a subject of the present invention.

[0032] Also with respect to all preferred compounds of the formula I all their stereoisomeric forms and mixtures thereof in any ratio and their physiologically acceptable salts explicitly are a subject of the present invention, as well as are their prodrugs. Similarly, also in all preferred compounds of the formula I all residues that are present more than one time in the molecule are independent of each other and can be identical or different.

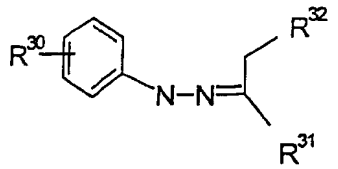
[0033] The compounds of the formula I can be prepared by utilizing procedures and techniques, which per se are well known and appreciated by one of ordinary skill in the art. Starting materials or building blocks for use in the general synthetic procedures that can be applied in the preparation of the compounds of formula I are readily available to one of ordinary skill in the art. In many cases they are commercially available or have been described in the literature. Otherwise they can be prepared from readily available precursor compounds analogously to procedures described in the literature, or by procedures or analogously to procedures described in this application.

[0034] In general, compounds of the formula I can be prepared, for example in the course of a convergent synthesis, by linking two or more fragments which can be derived retrosynthetically from the formula I. More specifically, suitably substituted starting indole derivatives are employed as building blocks in the preparation of the compounds of formula I. If not commercially available, such indole derivatives can be prepared according to the well-known standard procedures for the formation of the indole ring system such as, for example, the Fischer indole synthesis, the Madelung indole synthesis, the indole synthesis starting from N-chloroanilines and β-ketosulfides described by Gassman et al., the Bischler indole synthesis, the Reissert indole synthesis, or the Nenitzescu indole synthesis. By choosing suitable precursor molecules, these indole syntheses allow the introduction of a variety of substituents into the various positions of the indole system which can then be chemically modified in order to finally arrive at the molecule of the formula I having the desired substituent pattern. As one of the comprehensive reviews in which numerous details and literature references on the chemistry of indoles and on synthetic procedures for their preparation can be found, W. J. Houlihan (ed.),"Indoles, Part One", volume 25, 1972, out of the series "The Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor (ed.), John Wiley & Sons, is referred to.

[0035] Examples of the many commercially available indole derivatives that are suitable as starting materials for the preparation of the compounds of formula I, are the following (the acids listed are commercially available as the free acids themselves and/or as the methyl or ethyl esters): indole-2-carboxylic acid, indole-3-carboxylic acid, indole-3-acetic acid, 3-(3-indolyl)-propionic acid, indole-2,3-dicarboxylic acid, 3-ethoxycarbonylmethyl-indole-2-carboxylic acid, 3-methyl-indole-2-carboxylic acid, 5-fluoroindole-2-carboxylic acid, 5-chloro-indole-2-carboxylic acid, 5-bromo-indole-2-carboxylic acid, 5-methoxy-indole-2-carboxylic acid, 5-hydroxy-indole-2-carboxylic acid, 5,6-dimethoxy-indole-2-carboxylic acid, 4-benzyloxy-indole-2-carboxylic acid, 5-benzyloxy-indole-2-carboxylic acid, 6-benzyloxy-5-methoxy-indole-2-carboxylic acid, 5-methyl-indole-2-carboxylic acid, 5-ethylindole-2-carboxylic acid, 7-methyl-indole-2-carboxylic acid, 4-methoxy-indole-2-carboxylic acid, 6-methoxy-indole-2-carboxylic acid, 4,6-dimethoxy-indole-2-carboxylic acid, 4,6-dichloro-indole-2-carboxylic acid, 5-nitro-indole-2-carboxylic acid, 5-methylsulfonyl-indole-2-carboxylic acid, 7-nitro-indole-2-carboxylic acid, 7-tert-butylcarbonylamino-indole-2-carboxylic acid, 7-(3-trifluoro-methylbenzoylamino)-indole-2-carboxylic acid, 7-(4-methoxyphenylsulfonylamino)-indole-2-carboxylic acid, 5-bromo-3-methyl-indole-2-carboxylic acid, 3-(2-carboxyethyl)-6-chloroindole-2-carboxylic acid.

[0036] If starting indole derivatives are to be synthesized this can be done, for example, according to the well known indole syntheses mentioned above. In the following they are explained briefly, however, they are standard procedures comprehensively discussed in the literature, and are well known to one skilled in the art.

[0037] The Fischer indole synthesis comprises the acid cyclization of phenylhydrazones, for example of the general formula **2**,



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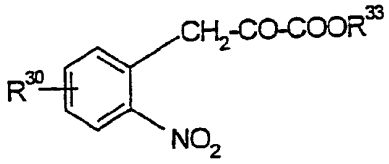
which can be obtained by various methods and in which R^{30}, R^{31} and R^{32} and n can have a wide variety of denotations. Besides hydrogen and alkyl, R^{31} and R^{32} can especially denote ester groups or methyl or ethyl groups or 2,2,2- trif-

luoroethyl groups carrying an ester group as substituent thus allowing the introduction into the indole molecule of the $(CH_2)_p$-CO moiety occurring in the groups R^2 and/or R^3 in the compounds of the formula I. As examples of the many literature references describing the synthesis of indole derivatives according to the Fischer synthesis, besides the above-mentioned book edited by Houlihan, the following articles are mentioned: F.G. Salituro et al., J. Med. Chem. 33 (1990) 2944; N.M. Gray et al., J. Med. Chem. 34 (1991) 1283; J. Sh. Chikvaidze et al., Khim. Geterotsikl. Soedin. (1991) 1508; S. P. Hiremath et al., Indian J. Chem. 19 (1980) 770; J. Bornstein, J. Amer. Chem. Soc. 79 (1957) 1745; S. Wagaw, B. Yang and S. Buchwald, J. Am. Chem. Soc. 121 (1999) 10251 or by Y. Murakami, Y. Yokoyama, T. Miura, H. Hirasawa Y. Kamimura and M. Izaki, Heterocycles 22 (1984) 1211.

[0038] The Reissert indole synthesis comprises the reductive cyclization of o-nitrophenylpyruvic acids or esters thereof, for example of the general formula 3,

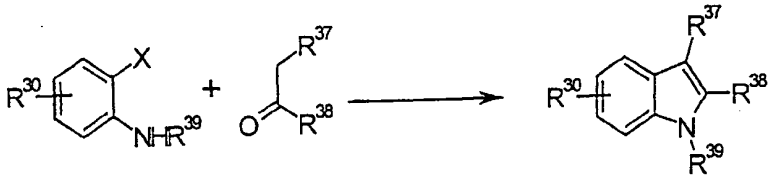


3

in which the groups R^{30} can have a wide variety of denotations and can be present in all positions of the benzene ring. The Reissert indole synthesis leads to derivatives of indole-2-carboxylic acids. The pyruvic acid derivatives of the formula **3** can be obtained by condensation of oxalic acid esters with substituted o-nitrotoluenes. As literature references, besides the above-mentioned book edited by Houlihan and the literature articles mentioned therein, for example the articles by H. G. Lindwall and G. J. Mantell, J. Org. Chem. 18 (1953) 345 or by H. Burton and J. L. Stoves, J. Chem. Soc. (1937) 1726 or by W. Noland, F. Baude, Org. Synth Coll. Vol. V, J. Wiley, New York, (1973) 567 are mentioned. Another method to gain access to the indole structure involves palladium catalysis, for example o-haloanilines of the general formula **4** can be cyclized to indoles utilizing several alkynes according to J. Ezquerra, C. Pedregal. C. Lamas, J. Barluenga, M. Pérez, M. Garcia-Martin, J. Gonzalez, J. Org. Chem. 61 (1996) 5805; or R. Larock, E. Yum, M. Refvik, J. Org. Chem. 63 (1998) 7653; or F. Ujjainwalla, D. Warner, Tetrahedron Lett. 39 (1998) 5355 and furthermore A. Rodriguez, C. Koradin, W. Dohle, P. Knochel, Angew. Chem. 112 (2000) 2607:

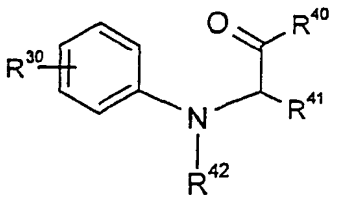
4 **5** **6**

[0039] Alternatively the indole structure can be built up by employment of a variety of ketones under palladium catalysis according to C. Chen, D. Liebermann, R. Larsen, T. Verhoeven and P. Reider J. Org. Chem. 62 (1997) 2676 as indicated below:



7 **8** **9**

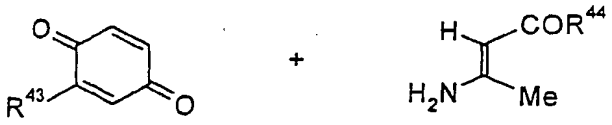
[0040] According to the Bischler indole synthesis α-anilinoketones, for example of the general formula **10**,



10

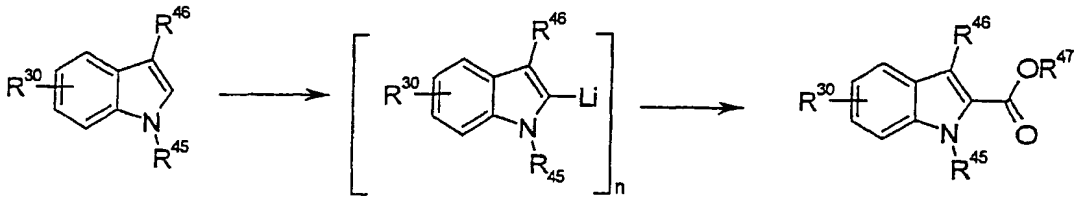
can be cyclized to indole derivatives.

[0041] The Nenitzescu indole synthesis provides a valuable route to indole-3-carboxylic acid derivatives carrying a hydroxy group in the 5-position. It comprises the reaction of a para-benzoquinone with a β-aminocrotonate, for example of the compounds of the formulae **11** and **12**.



11 **12**

[0042] A further route to specifically substituted indole derivatives proceeds via 2,3-dihydroindoles (indolines) which can be easily obtained by reduction of indoles, for example by hydrogenation, or by cyclization of suitable phenylethylamine derivatives. Indolines can undergo a variety of electrophilic aromatic substitution reaction allowing the introduction of various substituents into the benzene nucleus which cannot directly be introduced by such reactions into the benzene nucleus of the indole molecule. The indolines can then be dehydrogenated to the corresponding indoles, for example with reagents like chloranil, or palladium together with a hydrogen acceptor. Again, details on these syntheses can be found in the above-mentioned book edited by Houlihan. Moreover 2-H-indoles can be converted into the corresponding carboxylic acids or carboxylic esters by lithiation of the 2-position of the indoles of the general formula **13** and subsequent reaction with carbon dioxide or alkylchloroformate according to I. Hasan, E. Marinelli, L. Lin, F. Fowler, A. Levy, J. Org. Chem. 46 (1981) 157; T. Kline J. Heterocycl. Chem. 22 (1985) 505; J.-R. Dormoy, A. Heymes, Tetrahedron 49, (1993) 2885; E. Desarbre, S. Coudret, C. Meheust, J.-Y. Mérour, Tetrahedron 53 (1997) 3637 as indicated below:



13 **16** **17**

[0043] R^{45} denotes for Hydrogen or a protecting group like for example benzenesulfonyl or tert-butoxycarbonyl. Depending on the substituents in the starting materials, in certain indole syntheses mixtures of positional isomers may be obtained which, however, can be separated by modern separation techniques like, for example, preparative HPLC.

[0044] Further, in order to obtain the desired substituents in the benzene nucleus and in the heterocyclic nucleus of the indole ring system in the formula I, the functional groups introduced into the ring system during the indole synthesis can be chemically modified. For example, indoles carrying a hydrogen atom in the 2-position or the 3-position can also be obtained by saponification and subsequent decarboxylation of indoles carrying an ester group in the respective

position. Carboxylic acid groups and acetic acid groups in the 2-position and the 3-position can be converted into their homologues by usual reactions for chain elongation of carboxylic acids. Halogen atoms can be introduced into the 2-position or the 3-position, for example by reacting the respective indolinone with a halogenating agent such as phosphorus pentachloride analogously to the method described by J. C. Powers, J. Org. Chem. 31 (1966) 2627. The starting indolinones for such a synthesis can be obtained from 2-aminophenyl acetic acids. Starting indole derivatives for the preparation of compounds of the formula I carrying a halogen substituent in the 3-position can also be obtained according to procedures described in the literature like the following. For the fluorination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position N-fluoro-2,4,6-trimethylpyridinium triflate is the reagent of choice (T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita J. Am. Chem. Soc. 112 (1990) 8563). Chlorination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position by reaction with sulfuryl chloride in benzene yields 3-chloro-1 H-indole-2-carboxylic acid ethyl ester (Chem. Abstr. 1962, 3441 i - 3442b); the same result can obtained by means of NCS (D. Comins, M. Killpack, Tetrahedron Lett. 33 (1989) 4337; M. Brennan, K. Erickson, F. Szmlac, M. Tansey, J. Thornton, Heterocycles 24 (1986) 2879). Bromination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position can be achieved by reaction with NBS (M. Tani, H. Ikegami, M. Tashiro, T. Hiura, H. Tsukioka, Heterocycles 34 (1992) 2349). Analogously to the procedures described above NIS can be used efficiently for the iodination in the of 1 H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position. Furthermore the iodination of 1H-indole-2-carboxylic acid ethyl ester derivatives in the 3-position the use of iodine is efficient (T. Sakamoto, T. Nagano, Y. Kondo, H. Yamanaka Chem. Pharm. Bull. 36 (1988) 2248).

Especially the groups present in the indole ring system can be modified by a variety of reactions and thus the desired residues R^{1a}, R^{1b}, R^{1c}, R^{1d} and R^{1e} be obtained. For example, nitro groups can be reduced to amino group with various reducing agents, such as sulfides, dithionites, complex hydrides or by catalytic hydrogenation. A reduction of a nitro group may also be carried out at a later stage of the synthesis of a compound of the formula I, and a reduction of a nitro group to an amino group may also occur simultaneously with a reaction performed on another functional group, for example when reacting a group like a cyano group with hydrogen sulfide or when hydrogenating a group. In order to introduce the residues R^{5a}, R^{5b} and R^{6a}-SO_2, amino groups can then be modified according to standard procedures for alkylation, for example by reaction with (substituted) alkyl halogenides or by reductive amination of carbonyl compounds, according to standard procedures for acylation, for example by reaction with activated carboxylic acid derivatives such as acid chlorides, anhydrides, activated esters or others or by reaction with carboxylic acids in the presence of an activating agent, or according to standard procedures for sulfonylation, for example by reaction with sulfonyl chlorides. Halogens or hydroxy groups - via the triflate or nonaflate - or primary amines - via its diazonium salt - or after interconversion to the corresponding stannane, or boronic acid - present in the indole structure can be converted into a variety of other functional groups like for example -CN, -CF_3, Ethers, acids, amides, amines, alkyl- or aryl groups mediated by means of transition metals, namely palladium or nickel catalysts or copper salts and reagents for example referred to below (F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 110 (1998) 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 576 (1999) 125; T. Sakamoto, K. Ohsawa, J. Chem. Soc. Perkin Trans I, (1999), 2323; D. Nichols, S. Frescas, D. Marona-Lewicka, X. Huang, B. Roth, G. Gudelsky, J. Nash, J. Med. Chem, 37 (1994), 4347; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett., 39 (1998) 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 39 (1998) 2933; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994)

[0045] Ester groups present in the benzene nucleus can be hydrolyzed to the corresponding carboxylic acids, which after activation can then be reacted with amines or alcohols under standard conditions. Ether groups present at the benzene nucleus, for example benzyloxy groups or other easily cleavable ether groups, can be cleaved to give hydroxy groups which then can be reacted with a variety of agents, for example etherification agents or activating agents allowing replacement of the hydroxy group by other groups. Sulfur-containing groups can be reacted analogously.

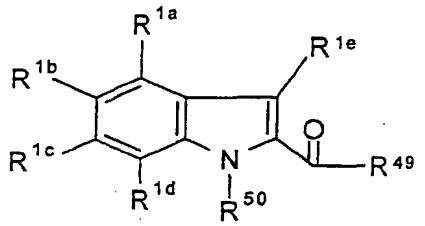
[0046] During the course of the synthesis in order to modify the groups R^{40} or $R^{8'}$ attached to the indole ring system by application of parallel synthesis methodology, beside a variety of reactions, palladium catalysis can be extremely useful. Such reactions are described for example in F. Diederich, P. Stang, Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1998; or M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH, 1998; J. Tsuji, Palladium Reagents and Catalysts, Wiley, 1996; J. Hartwig, Angew. Chem. 110 (1998), 2154; B. Yang, S. Buchwald, J. Organomet. Chem. 576 (1999) 125; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, Tetrahedron Lett. 39 (1998) 2941; D. Chan, K. Monaco, R. Wang, M. Winters, Tetrahedron Lett. 39 (1998) 2933; J. Wolfe, H. Tomori, J. Sadight, J. Yin, S. Buchwald, J. Org. Chem. 65 (2000) 1158; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, 1994.

[0047] The previously-mentioned reactions for the conversion of functional groups are furthermore, in general, extensively described in textbooks of organic chemistry like M. Smith, J. March, March's Advanced Organic Chemistry, Wiley-VCH, 2001 and in treatises like Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany, or "Organic Reactions", John Wiley & Sons, New York, or R. C. Larock,

" Comprehensive Organic Transformations", Wiley-VCH, 2nd ed (1999), B. Trost, I. Fleming (eds.) Comprehensive Organic Synthesis, Pergamon,1991; A. Katritzky, C. Rees, E. Scriven Comprehensive Heterocyclic Chemistry II, Elsevier Science, 1996) in which details on the reactions and primary source literature can be found. Due to the fact that in the present case the functional groups are attached to an indole ring it may in certain cases become necessary to specifically adapt reaction conditions or to choose specific reagents from a variety of reagents that can in principle be employed into a conversion reaction, or otherwise to take specific measures for achieving a desired conversion, for example to use protection group techniques. However, finding out suitable reaction variants and reaction conditions in such cases does not cause any problems for one skilled in the art.

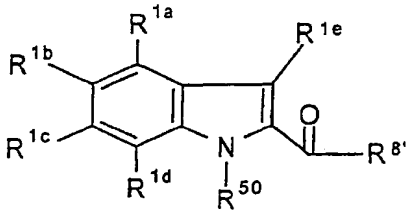
The structural elements present in the residues in the 1-position of the indole ring in the compounds of the formula I and in the COR^8 group present in the 2-position and/or in the 3-position of the indole ring can be introduced into the starting indole derivative obtainable as outlined above by consecutive reaction steps using parallel synthesis methodologies like those outlines below using procedures which per se are well known to one skilled in the art.

[0048] The residues $R^{8'}$ that can be introduced in formula **14**, for example, by condensing a corresponding carboxylic acid of the formula **14** with a compound of the formula $HR^{8'}$, i. e. with an amine of the formula $HN(R^{1'})R^{2'}$-V-G-M to give a compound of the formula **15**. The compound of the formula **15** thus obtained can already contain the desired final groups, i. e. the groups $R^{8'}$ and R^{50} can be the groups $-N(R^1)R^2$-V-G-M and R^0-Q- as defined in the formula I, or optionally in the compound of the formula **15** thus obtained subsequently the residue or the residues $R^{8'}$ and the residue R^{50} are converted into the residues $-N(R^1)R^2$-V-G-M and R^0-Q-, respectively, to give the desired compound of the formula I.



$HR^{8'}$

14



formula I

15

[0049] Thus, the residues $R^{8'}$ and the residues $R^{1'}$ and $R^{2'}$-V-G-M contained therein can have the denotations of R^1 and R^2-V-G-M, respectively, given above or in addition in the residues $R^{1'}$ and $R^{2'}$-V-G-M functional groups can also be present in the form of groups that can subsequently be transformed into the final groups R^1 and R^2-V-G-M, i. .e. functional groups can be present in the form of precursor groups or of derivatives, for example in protected form. In the course of the preparation of the compounds of the formula I it can generally be advantageous or necessary to introduce functional groups which reduce or prevent undesired reactions or side reactions in the respective synthesis step, in the form of precursor groups which are later converted into the desired functional groups, or to temporarily block functional groups by a protective group strategy suited to the synthesis problem. Such strategies are well known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, Wiley, 1991, or P. Kocienski, Protecting Groups, Thieme 1994). As examples of precursor groups nitro groups and cyano groups may be mentioned which can in a later step be transformed into carboxylic acid derivatives or by reduction into aminomethyl groups, or nitro groups which may be transformed by reduction like catalytic hydrogenation into amino groups

by reduction. Protective groups can also have the meaning of a solid phase, and cleavage from the solid phase stands for the removal of the protective group. The use of such techniques is known to those skilled in the art (Burgess K (Ed.) Solid Phase Organic Synthesis ,New York: Wiley, 2000). For example, a phenolic hydroxy group can be attached to a trityl-polystyrene resin, which serves as a protecting group, and the molecule is cleaved from this resin by treatment with TFA at a later stage of the synthesis.

[0050] The residue R^{50} in the compounds of the formulae **14** and **15** can denote the group -Q-R^0 as defined above which finally is to be present in the desired target molecule of the formula I, or it can denote a group which can subsequently be transformed into the group -Q-R^0, for example a precursor group or a derivative of the group -Q-R^0 in which functional groups are present in protected form, or R^{50} can denote a hydrogen atom or a protective group for the nitrogen atom of the indole ring. Similarly, the residues R^{1e}, R^{1a}, R^{1b}, R^{1c} and R^{1d} in the formulae **14** and **15** have the corresponding definitions of R^7, R^6, R^5, R^4, and R^3 in formula I as defined above, however, for the synthesis of the compounds of the formula I these residues, too, can in principle be present at the stage of the condensation of a compound of the formula **14** with a compound of the formula $HR^{8'}$ giving a compound of the formula **15** in the form of precursor groups or in protected form.

[0051] The residues R^{49} in the compounds of the formula **14** which can be identical or different, can be, for example, hydroxy or (C_1-C_4)-alkoxy, i. e., the groups COR^{49} present in the compounds of the formula **14** can be, for example, the free carboxylic acids or esters thereof like alkyl esters as can be the groups COR^8 in the compounds of the formula I. The groups COR^{49} can also be any other activated derivative of a carboxylic acid which allows amide formation, ester formation or thioester formation with a compound of the formula $HR^{8'}$. The group COR^{49} can be, for example, an acid chloride, an activated ester like a substituted phenyl ester, an azolide like an imidazolide, an azide or a mixed anhydride, for example a mixed anhydride with a carbonic acid ester or with a sulfonic acid, which derivatives can all be prepared from the carboxylic acid by standard procedures and can be reacted with an amine, an alcohol or a mercaptan of the formula $HR^{8'}$ under standard conditions. A carboxylic acid group COOH representing COR^{49} in a compound of the formula **14** can be obtained, for example, from an ester group introduced into the indole system during an indole synthesis by standard hydrolysis procedures.

[0052] Compounds of the formula I in which a group COR^8 is an ester group can also be prepared from compounds of the formula **14** in which COR^{49} is a carboxylic acid group by common esterification reactions like, for example, reacting the acid with an alcohol under acid catalysis, or alkylation of a salt of the carboxylic acid with an electrophile like an alkyl halogenide, or by transesterification from another ester. Compounds of the formula I in which a group COR^8 is an amide group can be prepared from amines and compounds of the formula **14** in which COR^{49} is a carboxylic acid group or an ester thereof by common amination reactions. Especially for the preparation of amides the compounds of the formula **14** in which COR^{49} is a carboxylic acid group can be condensed under standard conditions with compounds of the formula $HR^{8'}$ which are amines by means of common coupling reagents used in peptide synthesis. Such coupling reagents are, for example, carbodiimides like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide, carbonyldiazoles like carbonyldiimidazole (CDI) and similar reagents, propylphosphonic anhydride, O-((cyano-(ethoxycarbonyl)-methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU), diethylphosphoryl cyanide (DEPC) or bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride (BOP-Cl) and many others.

[0053] If the residue -Q-R^0 present in an indole of the formula I or the residue R^{50} present in an indole of the formula **14**, or a residue in which functional groups within the residue -Q-R^0 or R^{50} are present in protected form or in the form of a precursor group, have not already been introduced during a preceding step, for example during a synthesis of the indole nucleus, these residues can, for example, be introduced into the 1-position of the indole system by conventional literature procedures well known to one skilled in the art for N-alkylation, reductive amination, N-arylation, N-acylation or N-sulfonylation of ring nitrogen atoms of heterocycles. The starting indole derivative that is to be employed in such a reaction carries a hydrogen atom in the 1-position. N-Alkylation of a ring nitrogen atom can, for example, be performed under standard conditions, preferably in the presence of a base, using an alkylating compound of the formula LG-Q-R^0 or of the formula R^{50}-LG, wherein the atom in the group Q or in the group R^{50} bonded to the group LG in this case is an aliphatic carbon atom of an alkyl moiety and LG is a leaving group, for example halogen like chlorine, bromine or iodine, or a sulfonyloxy group like tosyloxy, mesyloxy or trifluormethylsulfonyloxy. LG may, for example, also be a hydroxy group which, in order to achieve the alkylation reaction, is activated by a conventional activating agent. For the preparation of compounds in which A is a direct linkage and an aromatic group is directly bonded to the 1-position of the indole system, conventional arylation procedures can be used. For example aryl fluorides like alkyl fluorobonzoates or 4-fluorophenyl methyl sulfones can be employed as arylating agents. Such processes are described, for example, By S. Stabler, Jahangir, Synth. Commun. 24 (1994) 123; I. Khanna, R. Weier, Y. Yu, X. Xu. F. Koszyk, J. Med. Chem. 40 (1997) 1634. Alternatively a wide variety of substituted aryl iodides, aryl bromides or aryl triflates can serve as arylating agents at the 1-position of the indole system in a copper salt or palladium mediated reaction according to R. Sarges, H. Howard, K. Koe, A. Weissmann, J. Med. Chem, 32 (1989) 437; P. Unangst, D. Connor, R. Stabler, R. Weikert, J. Heterocycl. Chem, 24 (1987) 811; G. Tokmakov, I. Grandberg, Tetrahedron 51 (1995) 2091; D. Old, M. Harris, S. Buchwald, Org. Lett. 2 (2000) 1403, G. Mann, J. Hartwig, M. Driver, C. Fernandez-Rivas, J. Am. Chem. Soc.

120 (1998) 827; J. Hartwig, M. Kawatsura, S. Hauk, K. Shaughnessy, L. J. Org. Chem. 64 (1999) 5575. Moreover such arylations can also be accomplished by reaction of a wide range of substituted aryl boronic acids as demonstrated for example by W. Mederski, M. Lefort, M. Germann, D. Kux, Tetrahedron 55 (1999) 12757.

[0054] Preferred methods include, but are not limited to those described in the examples.

[0055] The compounds of the present invention are serine protease inhibitors, which inhibit the activity of the blood coagulation enzyme factors Xa and/or factor VIIa. In particular, they are highly active inhibitors of factor Xa. They are specific serine protease inhibitors inasmuch as they do not substantially inhibit the activity of other proteases whose inhibition is not desired. The activity of the compounds of the formula I can be determined, for example, in the assays described below or in other assays known to those skilled in the art. With respect to factor Xa inhibition, a preferred embodiment of the invention comprises compounds which have a Ki $\leq$ 1 for factor Xa inhibition as determined in the assay described below, with or without concomitant factor VIIa inhibition, and which preferably do not substantially inhibit the activity of other proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the same concentration of the inhibitor). The compounds of the invention inhibit factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex.

[0056] The present invention also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation, inflammatory response or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for use in the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxis.

[0057] The present invention also relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances or excipients and/or auxiliary substances or additives.

[0058] The invention also relates to the treatment of disease states such as abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

[0059] The compounds of the formula I and their physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations which permit enteral or parenteral administration.

[0060] The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carriers being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, cornstarch or derivatives thereof, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 % to 90 % by weight of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg.

[0061] In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physicochemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

[0062] As inhibitors of factor Xa and/or factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the therapy and prophylaxis of conditions in which the activity of factor Xa and/or factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor Xa and/or factor VIIa or decreasing their activities, or for the prevention, alleviation or cure of which an inhibition of factor Xa and/or factor VIIa or a decrease in their activity is desired by the physician. As inhibition of factor Xa and/or factor VIIa influences blood coagulation and fibrinolysis, the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

[0063] Conditions in which a compound of the formula I can be favorably used include, for example, cardiovascular disorders, thromboembolic diseases or complications associated, for example, with infection or surgery. The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment or prophylaxis of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis, which can occur following surgery. In view of their pharmacological activity the compounds of the invention can replace or supplement other anticoagulant agents such as heparin. The use of a compound of the invention can result, for example, in a cost saving as compared to other anticoagulants.

When using the compounds of the formula I the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from 0.01 mg/kg to 100 mg/kg, preferably from 0.1 mg/kg to 50 mg/kg, in particular from 0.1 mg/kg to 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

[0064] A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample. Further, a compound of the formula I and its salts can be used for diagnostic purposes, for example in in vitro diagnoses, and as an auxiliary in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor Xa and/or factor VIIa or to isolate factor Xa and/or factor VIIa in a substantially purified form. A compound of the invention can be labeled with, for example, a radioisotope, and the labeled compound bound to factor Xa and/or factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used as a probe to detect the location or amount of factor Xa and/or factor VIIa activity in vivo, in vitro or ex vivo.

[0065] Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

[0066] The general synthetic sequences for preparing the compounds useful in the present invention our outlined in the examples given below. Both an explanation of, and the actual procedure for, the various aspects of the present invention are described where appropriate. The following examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known variations of the conditions and processes described in the examples can be used to synthesize the compounds of the present invention.

[0067] It is understood that changes that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Thus, the following examples are intended to illustrate but not limit the present invention.

Examples

[0068] When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tBu group or when a compound was purified by chromatography using an eluent which contained such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt or hydrochloric acid salt.

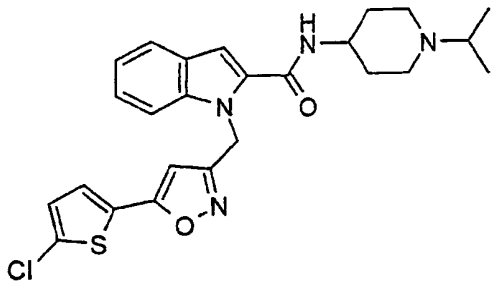
Abbreviations used:

[0069]

tert-Butyl	tBu
2,2'-bis(diphenylphoshino-1,1'-binaphthyl	Binap
Bis-(oxo-3-oxazolidinyl)-phosphoryl chloride	BOP-Cl
dibenzylidenacetone	dba
Dichloromethane	DCM
Diethylphosphoryl cyanide	DEPC
4-Dimethyaminopyridine	DMAP
N,N-Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
1,1'-Bis(diphenylphosphino)ferrocene	DPPF
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate	HATU
N-Bromosuccinimide	NBS
N-Chlorosuccinimide	NCS
N-Iodosuccinimide	NIS
N-Ethylmorpholine	NEM
Methanol	MeOH
Room temperature	RT
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA
O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborate	TOTU

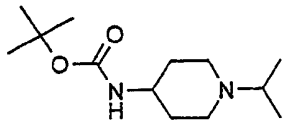
Example 1: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide

[0070]



(i) (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester

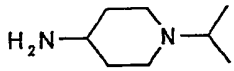
[0071]



[0072] To a solution of 5.0 g Piperidin-4-yl-carbamic acid tert-butyl ester in 15 ml methanol 7.34 ml acetone, 3.14 g $Na(CN)BH_3$ and 0.3 ml acetic acid were added. After stirring over night at RT the solvent was removed under reduced and the residue was partitioned between 30 ml of water and 30 ml ethylacetate. The organic layer was washed with saturated Na_2CO_3 solution, water and then dried over Na_2SO_4. The solvent was removed under reduced pressure and yields a white solid.
Yield: 4.8g MS (ES^+): m/e= 243.

(ii) 1-Isopropyl-piperidin-4-ylamine

[0073]



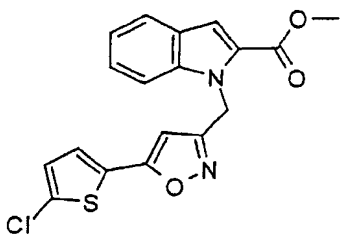
[0074] To 4.8 g (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester in 15 ml methanol 20 ml methanolic hydrochloric acid (8M) were added and the mixture was stirred over night. Removal of the solvent under reduced pressure yields a white solid, which was coevaporated twicely with 20 ml toluene. The product was obtained as its hydrochloride.
Yield: 5.42 g MS (ES^+): m/e= 143.

(iii) 1H-Indole-2-carboxylic acid methyl ester

[0075] To 2 g of 1H-Indole-2-carboxylic acid 15 ml of methanolic hydrochloric acid (8M) were added and the mixture was stirred at RT over night. After removal of the solvent under reduced pressure the residue was codestilled twicely with 10 ml toluene. The remaining slight yellow solid was subjected to the subsequent reaction without further purification.
Yield: 2.3g

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid methyl ester

[0076]



[0077] To a solution of 244.2 mg 1H-Indole-2-carboxylic acid methyl ester in 2 ml DMF 52.2 mg (60% in oil) sodium hydride were added at RT. After stirring for 30 min 500 mg 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] were added and the mixture was heated for 1h at 80°C. After subsequent cooling of the reaction to RT and addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure the residue was directly subjected to the subsequent saponification reaction without further purification.
Yield: 288 mg MS (ES^+): m/e= 373.

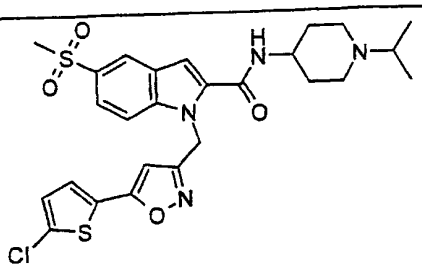
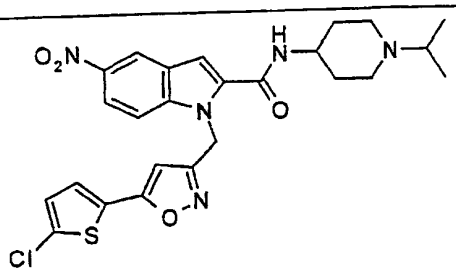
(v) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid

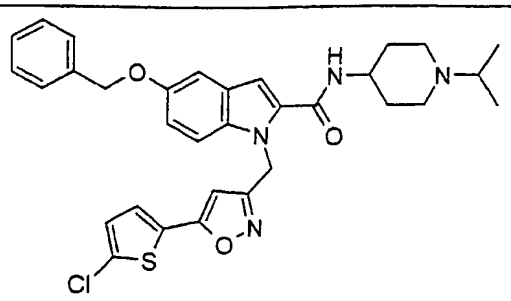
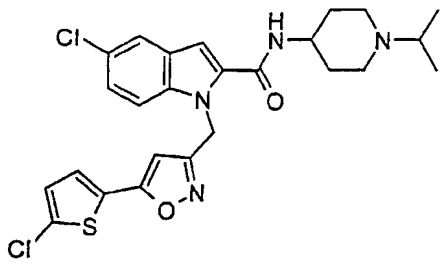
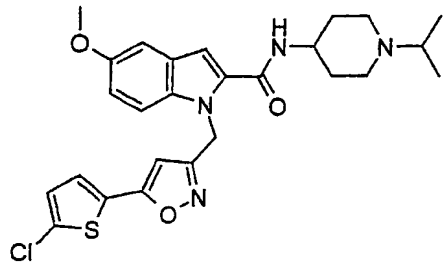
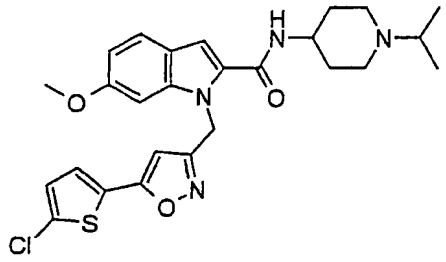
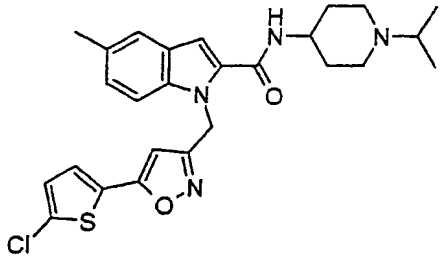
[0078] To a solution of 288 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid methyl ester in 10 ml THF 3 ml water and 57.0 mg lithium hydroxide monohydrate were added. After stirring for 2 h at 60°C the reaction was cooled to RT.The mixture was acidified with half concentrated hydrochloric acid and the precipitate collected by filtration and was washed with 3 ml water The product was obtained as a white solid which was dried under reduced pressure.
Yield: 253 mg MS (ES^+): m/e= 359, chloro pattern.

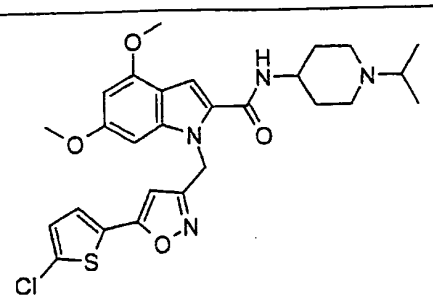
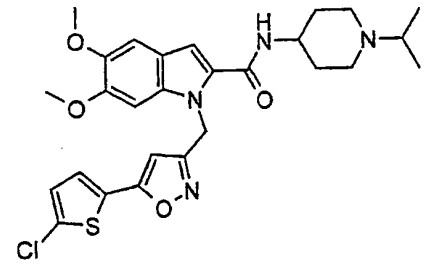
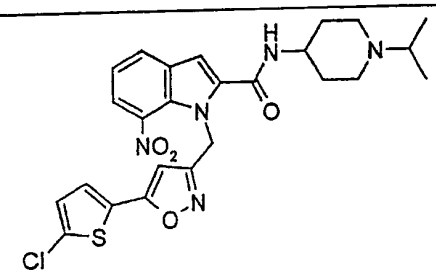
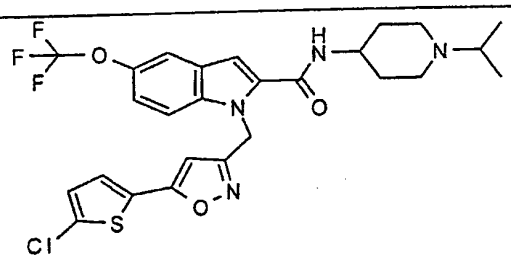
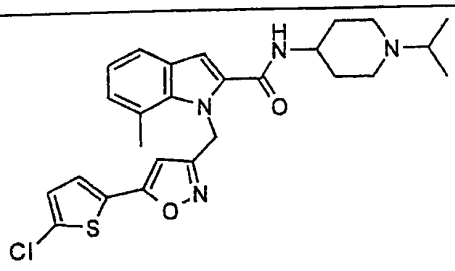
(vi) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

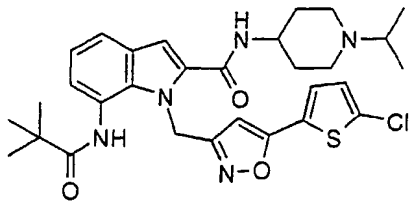
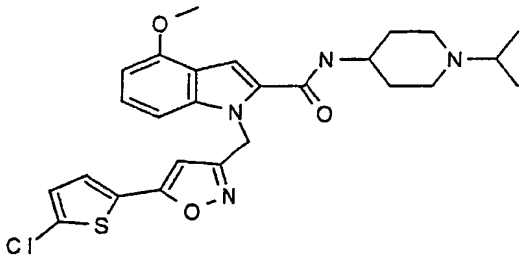
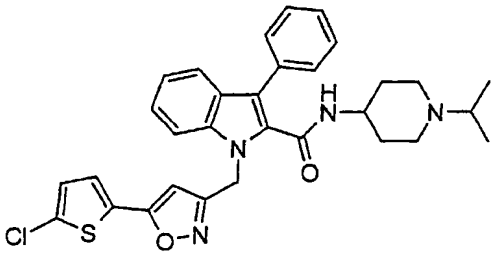
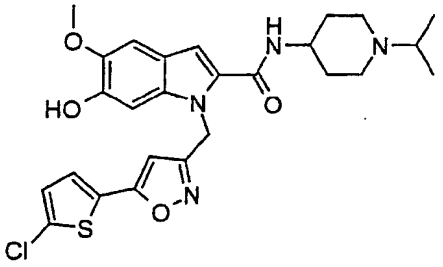
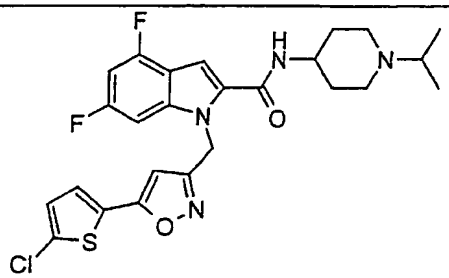
[0079] To a solution of 117 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid in 1 ml DCM and 0.17 ml NEt_3 76 mg BOP-Cl were added at RT and the mixture was stirred for 30 min. After addition of 81 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride the mixture was stirred over night. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.
Yield: 93 mg MS (ES^+): m/e= 483, chloro pattern.

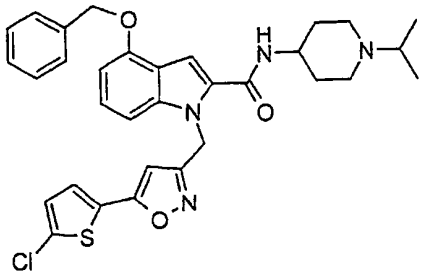
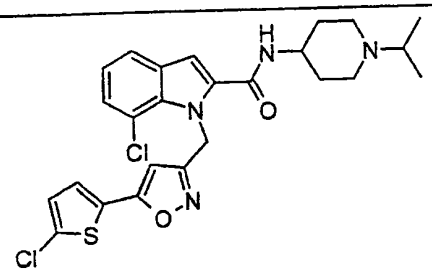
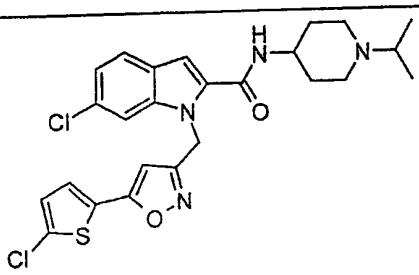
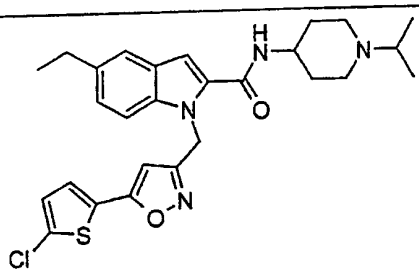
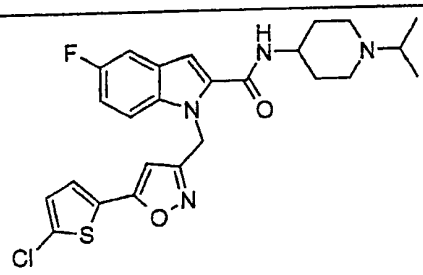
[0080] Analogously to Example 1 the following compounds were prepared by a similar procedure:

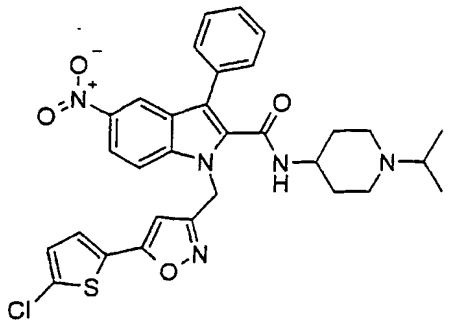
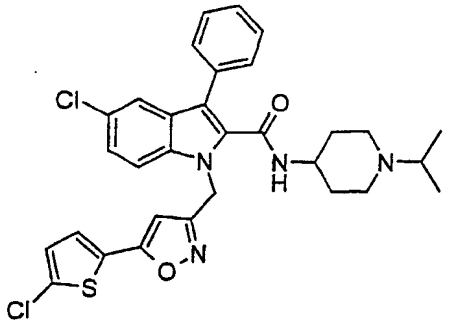
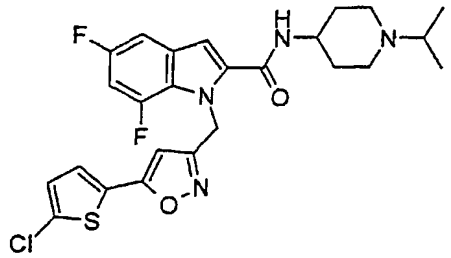
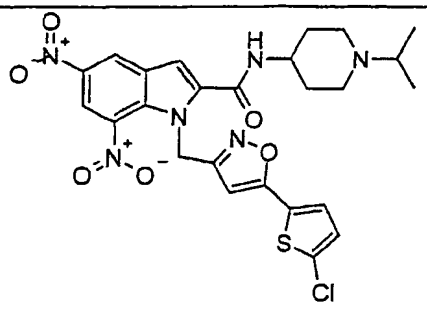
Example	Structure	MS (ESI+)
2		561, chloro pattern
3		528, chloro pattern

4		589, chloro pattern
5		517, chloro pattern
6		513, chloro pattern
7		513, chloro pattern
8		497, chloro pattern

9		543, chloro pattern
10		543, chloro pattern
11		528, chloro pattern
12		567, chloro pattern
13		497, chloro pattern

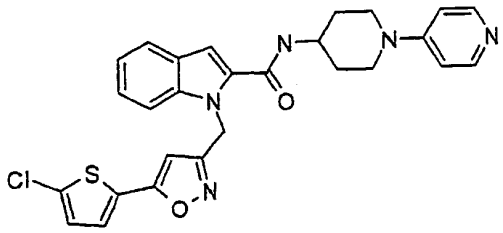
14		582, chloro pattern
15		513, chloro pattern
16		559, chloro pattern
17		529, chloro pattern
18		519, chloro pattern

19		589, chloro pattern
20		517, chloro pattern
21		517, chloro pattern
22		511, chloro pattern
23		501, chloro pattern

24		604, chloro pattern
25		593, chloro pattern
26		519, chloro pattern
27		573, chloro pattern

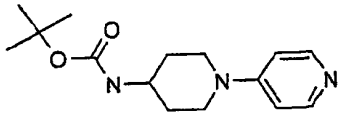
Example 28: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (3,4,5,6- tetrahydro-2H-[1,4']bipyridinyl-4-yl)-amide

[0081]



(i) (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-carbamic acid tert-butyl ester

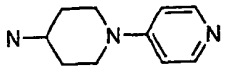
[0082]



[0083] A solution of 3 g Piperidin-4-yl-carbamic acid tert-butyl ester and 2.5 g 4- Chloropyridine in 9 ml n-butanol/water/NEt_3 1:1:1 was heated at 100 °C for 48 h. Then the solution was cooled to RT diluted with DCM and was washed with $NaHCO_3$ solution and then with water. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica with DCM as eluent yields after evaporation of the fractions containing the product a white foam.
Yield 1.7 g

(ii) 3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylamine

[0084]



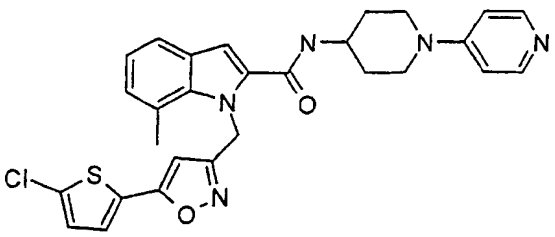
[0085] To a solution of 4 g (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-carbamic acid tert-butyl ester in 4 ml DCM, 12 ml TFA was added at RT. After stirring for 20 h the solution was diluted with 20 ml of toluene and was evaporated under reduced pressure. The residue was codestilled twice with toluene and then was used in the subsequent reactions without further purification. The product was obtained as its trifluoroacetate salt.
Yield: 2.7 g

(iii) 1-[5-(5-Chloro-th iophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (3,4,5,6- tetrahydro-2H-[1,4'] bipyridinyl-4-yl)-amide

[0086] The title compound was prepared analogously to Example 1 with the difference that 3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylamine was used instead of 1-Isopropylpiperidin-4-ylamine.
MS (ESI+): m/e= 518, chloro pattern.

Example 29: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-methyl-1H-indole-2-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-amide

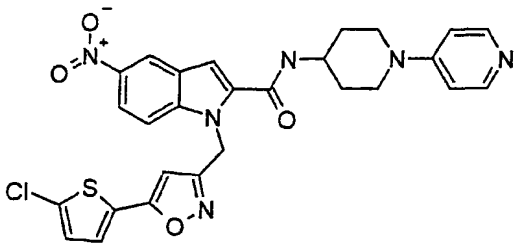
[0087]



[0088] The title compound was prepared analogously to Example 28 with the difference that 7-Methyl-1H-indole-2-carboxylic acid was used instead of 1H-Indole-2-carboxylic acid.
MS (ESI+): m/e = 532, chloro pattern.

Example 30: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-nitro-1H-indole-2-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-am ide

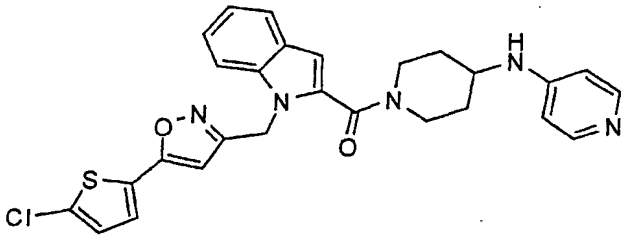
[0089]



[0090] The title compound was prepared analogously to Example 28 with the difference that 5-Nitro-1H-indole-2-carboxylic acid was used instead of 1H-Indole-2-carboxylic acid.
MS (ESI+): m/e = 563, chloro pattern.

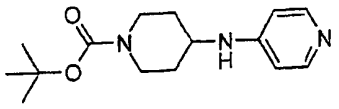
Example 31: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indol-2-yl}-[4-(pyridin-4- ylamino)-piperidin-1-yl]-methanone

[0091]



(i) 4-(Pyridin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester

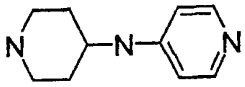
[0092]



[0093] A solution of 2.5 g 4-Amino-piperidine-1-carboxylic acid tert-butyl ester and 2.5 g 4-chloropyridine in 9 ml n-butanol/water/NEt_3 1:1:1 was heated at 100 °C for 85 h. Then the solution was cooled to RT was diluted with DCM and was washed with $NaHCO_3$ solution and water. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica with DCM as eluent yields, after evaporation of the fractions containing the product, a white foam.
Yield 1.7 g

(ii) Piperidin-4-yl-pyridin-4-yl-amine

[0094]



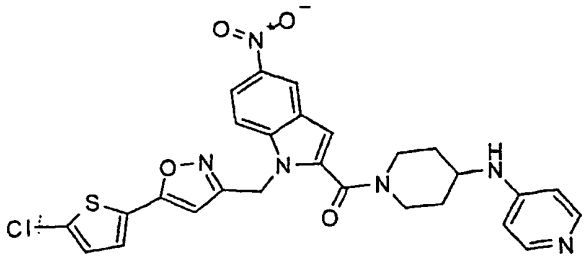
[0095] To a solution of 1.7 4-(Pyridin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester in 4 ml DCM 12 ml TFA was added at RT. After stirring for 20 h the solution was diluted with 20 ml of toluene and was evaporated under reduced pressure. The residue was codestilled twice with toluene and then it was used in the subsequent reactions without further purification. The product was obtained as its trifluoroacetate salt.
Yield: 4.0 g

(iii) {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indol-2-yl}-[4-(pyridin-4-ylamino)-piperidin-1-yl]-methanone

[0096] The title compound was prepared analogously to Example 1 with the difference that Piperidin-4-yl-pyridin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 518, chloro pattern.

Example 32: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-nitro-1H-indol-2-yl}-[4-(pyridin- 4-ylamino)-piperidin-1-yl]-methanone

[0097]

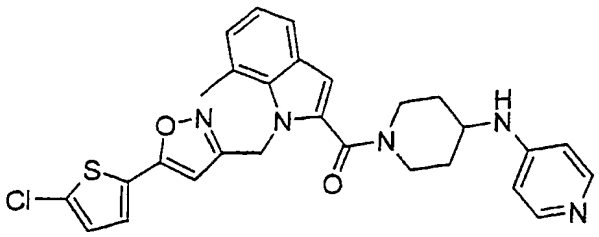


[0098] The title compound was prepared analogously to Example 31 with the difference that 5-Nitro-1 H-indole-

2-carboxylic acid was used instead of 1H-Indole-2-carboxylic acid.
MS (ESI+): m/e = 563, chloro pattern.

Example 33: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-methyl-1H-indol-2-yl}[4-(pyridin- 4-ylamino)-piperidin-1-yl]-methanone

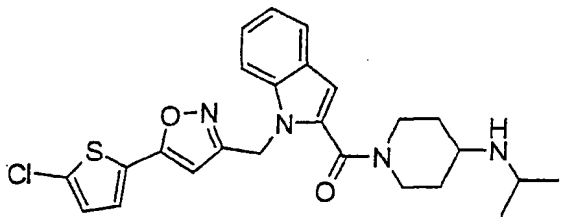
[0099]



[0100] The title compound was prepared analogously to Example 31 with the difference that 7-Methyl-1 H-indole-2-carboxylic acid was used instead of 1H-Indole-2-carboxylic acid.
MS (ESI+): m/e = 532, chloro pattern.

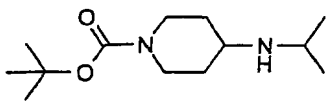
Example 34: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1 H-indol-2-yl}-(4-isopropylamino- piperidin-1-yl)-methanone

[0101]



(i) 4-Isopropylamino-piperidine-1-carboxylic acid tert-butyl ester

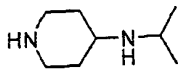
[0102]



[0103] To a solution of 1.5 g 4-Amino-piperidine-1-carboxylic acid tert-butyl ester in 20 ml acetonitrile 2.6 ml acetone, 0.94 g $Na(CN)BH_3$ and 0.3 ml acetic acid were added. After stirring over night at RT the solvent was removed under reduced and the residue was partitioned between 30 ml of water and 30 ml ethylacetate. The organic layer was washed with saturated Na_2CO_3 solution, water and then was dried over Na_2SO_4. Removal of the solvent under reduced pressure yields a white solid.
Yield: 2.8 g MS (ES^+): m/e= 243.

(ii) Isopropyl-piperidin-4-yl-amine

[0104]



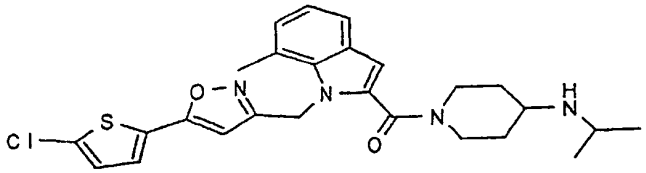
[0105] To a solution of 2.8 g 4-Isopropylamino-piperidine-1-carboxylic acid tert-butyl ester in 8 ml DCM 4 ml TFA was added at RT. After stirring for 20 h the solution was diluted with 20 ml of toluene and was evaporated under reduced pressure. The residue was codestilled twice with toluene and then it was used in the subsequent reactions without further purification. The product was obtained as its trifluoroacetate salt.
Yield: 4.4 g MS (ES+): m/e= 143.

(iii) {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indol-2-yl}-(4-isopropylaminopiperidin-1-yl)-methanone

[0106] The title compound was prepared analogously to Example 1 with the difference that Isopropyl-piperidin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 483, chloro pattern.

Example 35: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-methyl-1H-indol-2-yl}(4- isopropylamino-piperidin-1-yl)-methanone

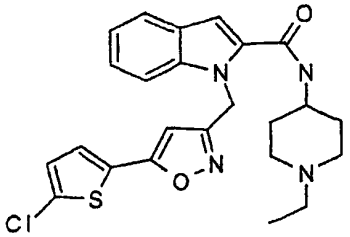
[0107]



[0108] The title compound was prepared analogously to Example 34 with the difference that 7-Methyl-1 H-indole-2-carboxylic acid was used instead of 1H-Indole-2-carboxylic acid.
MS (ESI+): m/e = 497, chloro pattern.

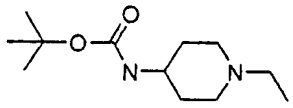
Example 36: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-ethyl- piperidin-4-yl)-amide

[0109]



(i) (1-Ethyl-piperidin-4-yl)-carbamic acid tert-butyl ester

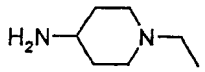
[0110]



[0111] To a solution of 5 g Piperidin-4-yl-carbamic acid tert-butyl ester in 20 ml methanol, 5.6 ml acetaldehyde, 3.2 g $Na(CN)BH_3$ and 3.2 g acetic acid were added. After stirring over night at RT the solvent was removed under reduced and the residue was partitioned between 30 ml of water and 200 ml ethylacetate. The organic layer was washed with saturated Na_2CO_3 solution, water and then it was dried over Na_2SO_4. Removal of the solvent under reduced pressure yields a white solid.
Yield: 4.4 g

(ii) 1-Ethyl-piperidin-4-ylamine

[0112]



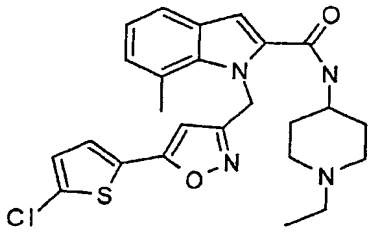
[0113] To 4.4 g (1-Ethyl-piperidin-4-yl)-carbamic acid tert-butyl ester in 15 ml methanol 20 ml methanolic hydrochloric acid (8M) was added and the mixture was stirred over night. Removal of the solvent under reduced pressure yields a white solid, which was coevaporated twice with 20 ml toluene. The product was obtained as its hydrochloride.
Yield: 4.3 g

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-ethyl-piperidin-4-yl)-amide

[0114] The title compound was prepared analogously to Example 1 with the difference that 1-Ethyl-piperidin-4-ylamine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 469, chloro pattern.

Example 37: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-methyl-1H-indole-2-carboxylic acid (1-ethyl-piperidin-4-yl)-amide

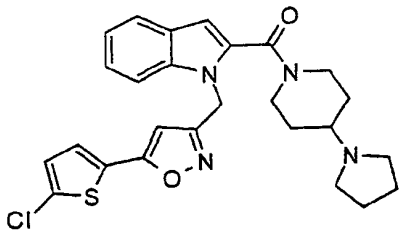
[0115]



[0116] The title compound was prepared analogously to Example 36 with the difference that 1-[57-methyl-1H-indole-2-carboxylic acid was used instead of 1H-Indole-2-carboxylic acid.
MS (ESI+): m/e = 483, chloro pattern.

Example 38: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indol-2-yl}-(4-pyrrolidin-1-yl- piperidin-1-yl)-methanone

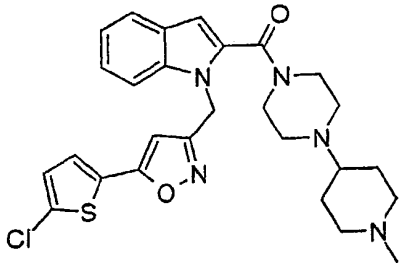
[0117]



[0118] The title compound was prepared analogously to Example 1 with the difference that 4-Pyrrolidin-1-yl-piperidine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 509, chloro pattern.

Example 39: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indol-2-yl}-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-methanone

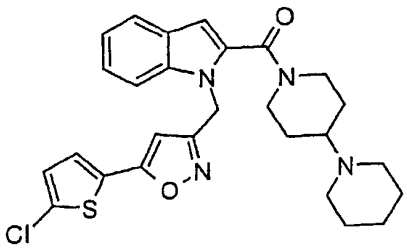
[0119]



[0120] The title compound was prepared analogously to Example 1 with the difference that 1-(1-Methyl-piperidin-4-yl)-piperazine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 524, chloro pattern.

Example 40: [1,4']Bipiperidinyl-1'-yl-{1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indol- 2-yl}-methanone

[0121]

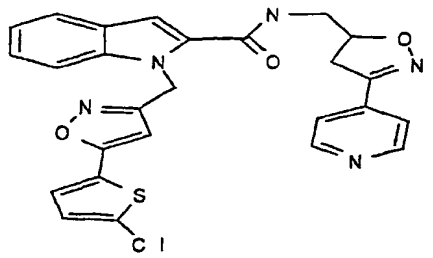


[0122] The title compound was prepared analogously to Example 1 with the difference that [1,4']bipiperidinyl was used instead of 1-Isopropyl-piperidin-4-ylamine.

MS (ESI+): m/e = 523, chloro pattern.

Example 41: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1 H-indole-2-carboxylic acid (3- pyridin-4-yl-4,5-dihydro-isoxazol-5-ylmethyl)-amide

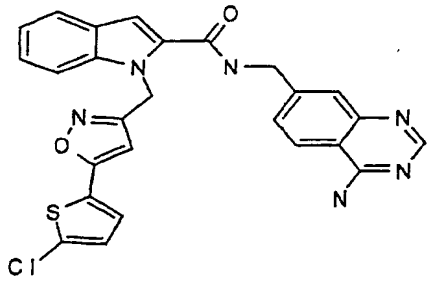
[0123]



[0124] The title compound was prepared analogously to Example 1 with the difference that C-(3-Pyridin-4-yl-4,5-dihydro-isoxazol-5-yl)-methylamine was used instead of 1-Isopropylpiperidin-4-ylamine. MS (ESI+): m/e = 518, chloro pattern.

Example 42: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (4-amino-quinazolin-7-ylmethyl)-amide

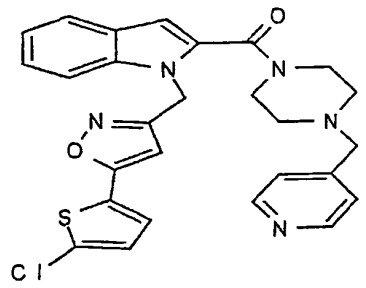
[0125]



[0126] The title compound was prepared analogously to Example 1 with the difference that 7-Aminomethyl-quinazolin-4-ylamine [Ewing, William R. et al. PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 515, chloro pattern.

Example 43: {1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1 H-indol-2-yl}-(4-pyridin-4- ylmethyl-piperazin-1-yl)-methanone

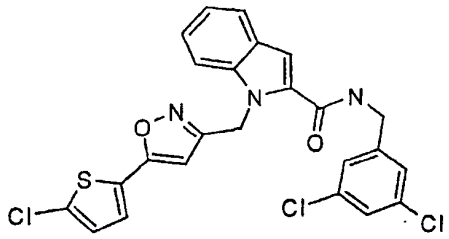
[0127]



[0128] The title compound was prepared analogously to Example 1 with the difference that 1-Pyridin-4-ylmethyl-piperazine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 518, chloro pattern.

Example 44: 1-[5-(5-Chloro-th iophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid 3,5-dichloro-benzylamide

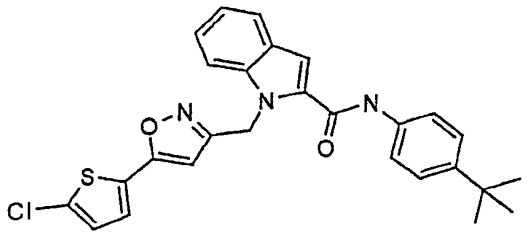
[0129]



[0130] The title compound was prepared analogously to Example 1 with the difference that 3,5-Dichloro-benzylamine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 516, chloro pattern.

Example 45: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (4- tert-butyl-phenyl)-amide

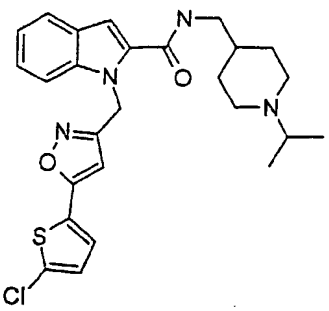
[0131]



[0132] The title compound was prepared analogously to Example 1 with the difference that 4tert-Butyl-phenylamine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 490, chloro pattern.

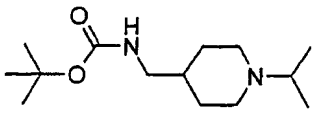
Example 46: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-ylmethyl)-amide

[0133]



(i) (1-Isopropyl-piperidin-4-ylmethyl)-carbamic acid tert-butyl ester

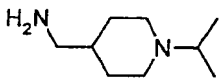
[0134]



[0135] To a solution of 1.0 g Piperidin-4-ylmethyl-carbamic acid tert-butyl ester in 20 ml acetonitrile 2.6 ml acetone and 586 mg $Na(CN)BH_3$ were added. After stirring over night at RT the solvent was removed under reduced and the residue was partitioned between 30 ml of water and 30 ml ethylacetate. The organic layer was washed with saturated Na_2CO_3 solution, water and then was dried over Na_2SO_4. Removal of the solvent under reduced pressure yields a white solid. Yield: 802 mg

(ii) C-(1-Isopropyl-piperidin-4-yl)-methylamine

[0136]



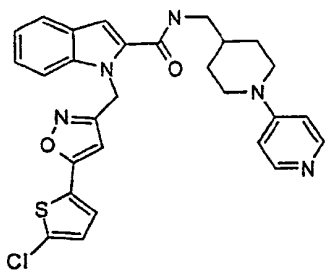
[0137] To a solution of 802 mg (1-Isopropyl-piperidin-4-ylmethyl)-carbamic acid tert-butyl ester in 5 ml DCM 4 ml TFA was added at RT. After stirring for 20 h the solution was diluted with 20 ml of toluene and was evaporated under reduced pressure. The residue was codestilled twice with toluene and then it was used in the subsequent reactions without further purification. The product was obtained as its trifluoroacetate salt. Yield: 1.7 g

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-ylmethyl)-amide

[0138] The title compound was prepared analogously to Example 1 with the difference that C-(1-Isopropyl-piperidin-4-yl)-methylamine was used instead of 1-Isopropyl-piperidin-4-ylamine. MS (ESI+): m/e = 496, chloro pattern.

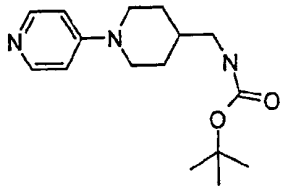
Example 47: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (3,4,5,6- tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-amide

[0139]



(i) (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-carbamic acid tBu ester

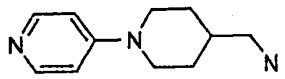
[0140]



[0141] A suspension of 5 g (23.3 mmol) Piperidin-4-ylmethyl-carbamic acid tBu ester 3.85 g (25.7 mmol) 4-Chloro-pyridin hydrochloride in 15 ml n-BuOH/H_2O/NEt_3 1:1:1 was refluxed for 3 days. After removal of the solvent under reduced pressure the residue was purified by chromatography on silica with DCM/MeOH 100:1 -> 50:1 ->10:1 - 5:1 and yields a white solid. Yield: 4.3 g

(ii) C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine

[0142]



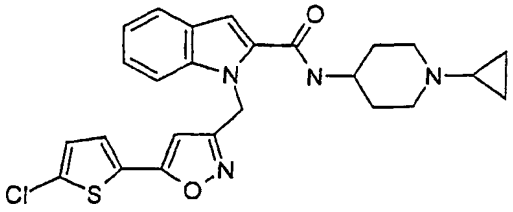
[0143] To a solution of 4.58 g (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-carbamic acid tBu ester in 12 ml DCM12 ml TFA was added at RT. After stirring for 30 min the solution was diluted with 20 ml of toluene and was evaporated under reduced pressure. The residue was codestilled twice with toluene and then it was used in the subsequent reactions without further purification. The product was obtained as its trifluoroacetate salt.
Yield: 3.3 g

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (3,4,5,6- tetrahydro-2H-[1,4'] bipyridinyl-4-ylmethyl)-amide

[0144] The title compound was prepared analogously to Example 1 with the difference that C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine was used instead of 1-Isopropyl-piperidin-4-ylamine. MS (ESI+): m/e = 532, chloro pattern.

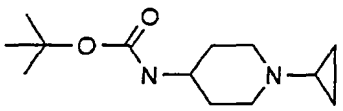
Example 48: 1-[5-(5-Chloro-th iophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1- cyclopropyl-piperidin-4-yl)-amide

[0145]



(i) (1-Cyclopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester

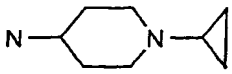
[0146]



[0147] To a suspension of 1 g Piperidin-4-yl-carbamic acid tert-butyl ester, 2 g freshly activated 3 Å mole sieve, 1 ml acetic acid, 6 ml 1-Ethoxycyclopropyl-oxy-trimethylsilane in 25 ml methanol 22.5 ml $Na(CN)BH_3$ (1M in THF) were added and the mixture was heated to reflux for 2 h. The reaction mixture was filtered trough a plug of celite, concentrated under reduced pressure and the residue was taken-up in ethyl acetate. The organic layer was washed with 1 M NaOH and saturated NaCl solution and finally was dried over Na_2SO_4. Evaporation of the solvents under reduced pressure yields a clear oil.
Yield: 1.44 g

(ii) 1-Cyclopropyl-piperidin-4-ylamine

[0148]



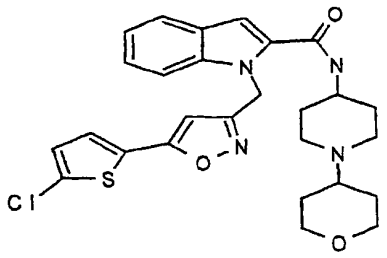
[0149] To a solution of 0.72 g (1-Cyclopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester in 5 ml DCM 3 ml TFA was added at RT. After stirring for 20 h the solution was diluted with 20 ml of toluene and the it was evaporated under reduced pressure. The residue was codestilled twice with toluene and then it was used in the subsequent reactions without further purification. The product was obtained as its trifluoroacetate salt.
Yield: 870 mg

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide

[0150] The title compound was prepared analogously to Example 1 with the difference that 1-Cyclopropyl-piperidin-4-ylamine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 481, chloro pattern.

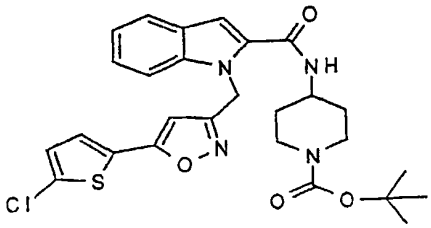
Example 49: 1-[5-(5-Chloro-th iophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid [1- (tetrahydro-pyran-4-yl)-piperidin-4-yl]-amide

[0151]



(i) 4-({1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester

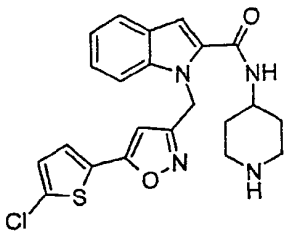
[0152]



[0153] To a solution of 1 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid, 1.4 ml N-NEM in 5 ml DCM 0.9 g TOTU were added and the mixture was stirred for 30 min at RT. Then 0.7 g 4-Amino-piperidine-1-carboxylic acid tert-butyl ester were added and the reaction was further stirred over night. After removal of the solvent under reduced pressure the residue was purified by chromatography on silica with ethyl acetate/heptane 4:1 as eluent. The fractions containing the product were evaporated and yield a white foam.
Yield: 1 g

(ii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid piperidin-4-ylamide

[0154]

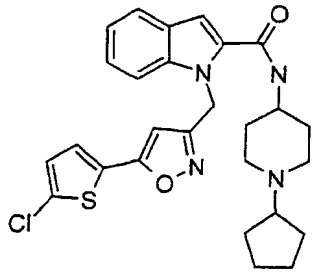
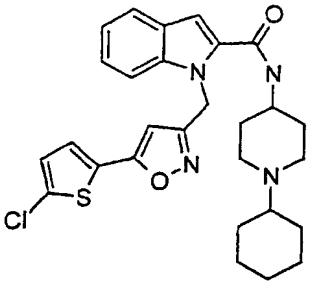


[0155] To 1 g of 4-({1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carbonyl}amino)-piperidine-1-carboxylic acid tert-butyl ester 10 ml of methanolic hydrochloric acid (8M) were added and the mixture was stirred at RT for 2 h. After removal of the solvent under reduced pressure the residue was codestilled twice with 10 ml toluene. The remaining slight yellow solid was subjected to the subsequent reaction without further purification. Yield: 0. 85 g

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid [1-(tetrahydro-pyran-4-yl)-piperidin-4-yl]-amide

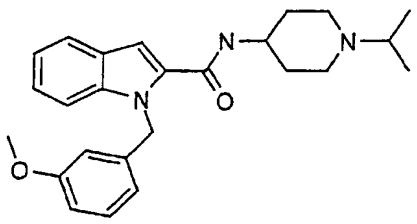
[0156] To a solution of 50 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid piperidin-4-ylamide and 35 mg Tetrahydro-pyran-4-one in 2 ml acetonitrile 14 mg $Na(CN)BH_3$ was introduced. After stirring at RT overnight the reaction mixture was concentrated under reduced pressure and was purified by preparative HPLC (C_{18} reverse phase column, elution with a H_2O/MeCN gradient with 0.5% TFA). The fractions containing the product were evaporated and lyophilized. The product was obtained as its trifluoroacetate salt.
Yield: 14 mg MS (ES+): m/e = 525, chloro pattern.

[0157] According to Example 49 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
50		495, chloro pattern
51		509, chloro pattern

Example 52: 1-(3-Methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

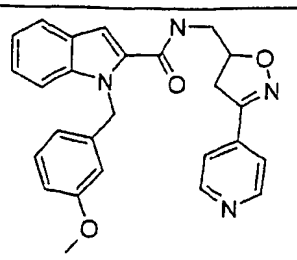
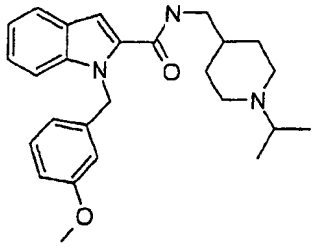
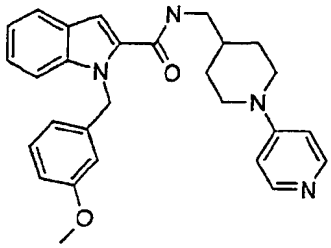
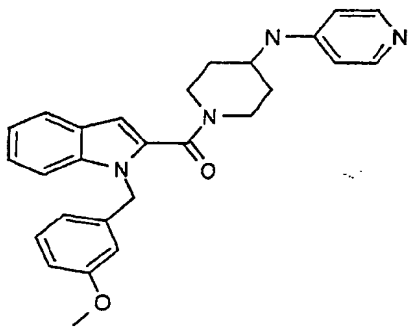
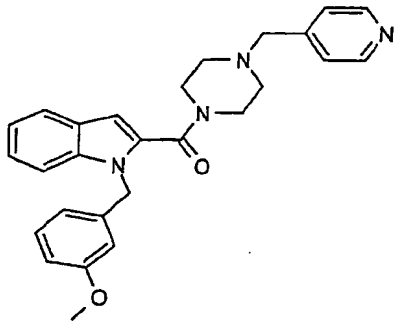
[0158]

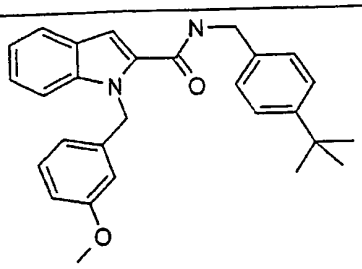
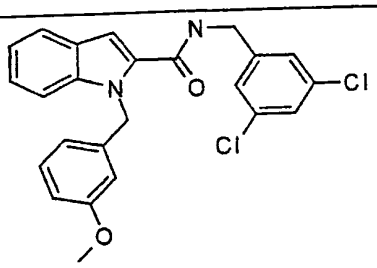
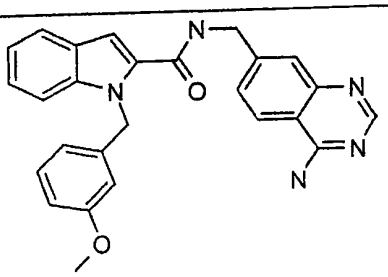
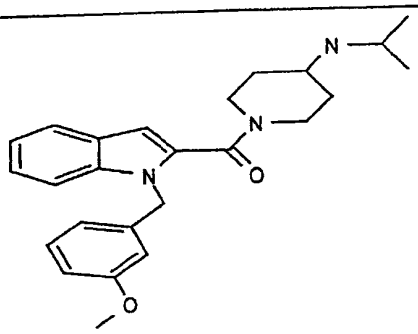
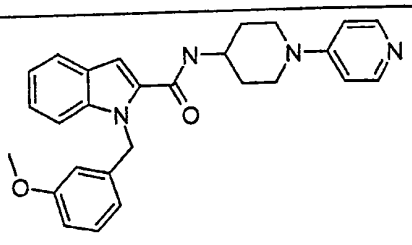


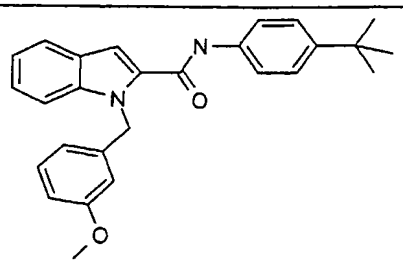
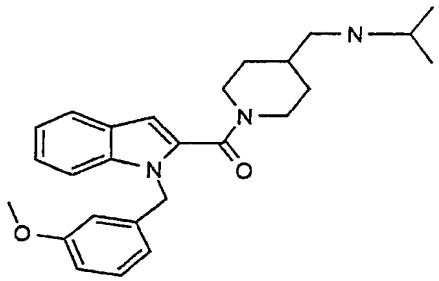
[0159] The title compound was prepared analogously to Example 1 with the difference that 1-Bromomethyl-3-methoxy-benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS (ESI+): m/e = 406.

[0160] According to Example 52 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)

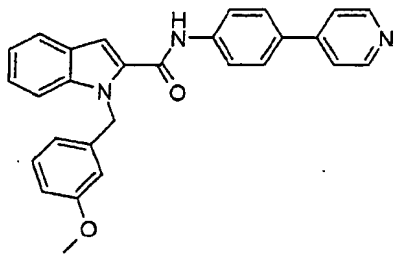
53		441
54		420
55		455
56		441
57		441

58		427
59		439, chloro pattern
60		438
61		405
62		441

63		413
64		420

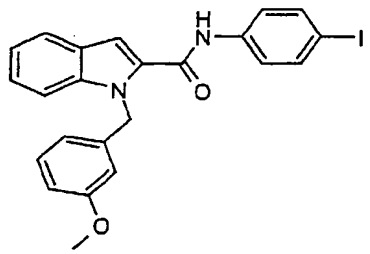
Example 65: 1-(3-Methoxy-benzyl)-1H-indole-2-carboxylic acid (4-pyridin-4-yl-phenyl)-amide

[0161]



(i) 1-(3-Methoxy-benzyl)-1H-indole-2-carboxylic acid (4-iodo-phenyl)-amide

[0162]



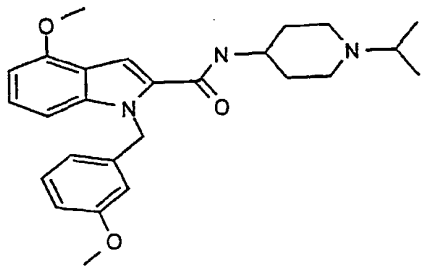
[0163] To a solution of 500 mg 1-(3-Methoxy-benzyl)-1 H-indole-2-carboxylic acid in 8 ml DCM and 0.9 ml NEt_3 452 mg BOP-Cl was added at RT and the mixture was stirred for 30 min. After addition of 583 mg 4-Iodo-phenylamine the mixture was stirred over night. Then the solvent was removed under reduced pressure to yield a white precipitate, which was washed with MeOH/DCM. Yield: 380 mg

(ii) 1-(3-Methoxy-benzyl)-1H-indole-2-carboxylic acid (4-pyridin-4-yl-phenyl)-amide

[0164] A solution of 100 mg 1-(3-Methoxy-benzyl)-1H-indole-2-carboxylic acid (4-iodo-phenyl)-amide, 31 mg 4-Pyridyl boronic acid and 200 µl aqueous Na_2CO_3 solution (2M) in 5 ml dimethoxyethane (dme) was purged with argon for 15 min. Then 20 mg $Pd(PPh_3)_4$ was added and the mixture was heated to 80°C over night. Finally, 3 ml saturated $NaHCO_3$ solution were added and the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After subsequent removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.
Yield: 15 mg MS(ESI+): m/e = 434.

Example 66: 4-Methoxy-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

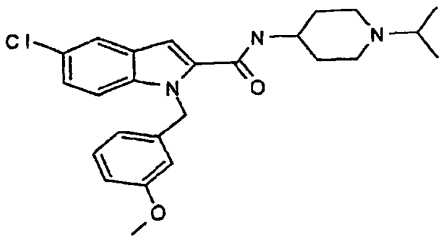
[0165]



[0166] The title compound was prepared analogously to Example 52 with the difference 4-Methoxy-1 H-indole-2-carboxylic acid was used instead of 1H-Indole-2-carboxylic acid. MS (ESI+): m/e = 436.

Example 67: 5-Chloro-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

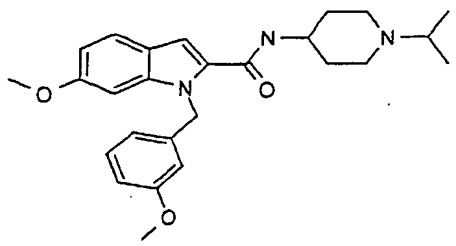
[0167]



[0168] The title compound was prepared analogously to Example 57 with the difference that 5-Chloro-1 H-indole-2-carboxylic acid was used instead of 1 H-indole-2-carboxylic acid.
MS (ESI+): m/e = 440, chloro pattern.

Example 68: 6-Methoxy-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

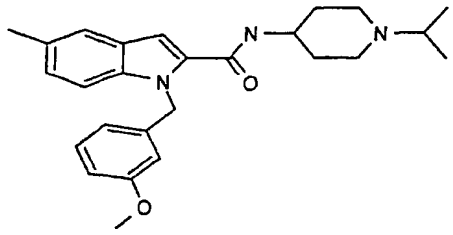
[0169]



[0170] The title compound was prepared analogously to Example 52 with the difference that 6-Methoxy-1 H-indole-2-carboxylic acid was used instead of 1H-indole-2-carboxylic acid. MS (ESI+): m/e = 436.

Example 69: 1-(3-Methoxy-benzyl)-5-methyl-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

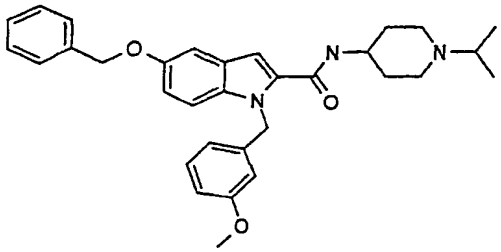
[0171]



[0172] The title compound was prepared analogously to Example 52 with the difference that 5-Methyl-1H-indole-2-carboxylic acid was used instead of 1H-indole-2-carboxylic acid.
MS (ESI+): m/e = 420.

Example 70: 5-Benzyloxy-1-(3-methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4- yl)-amide

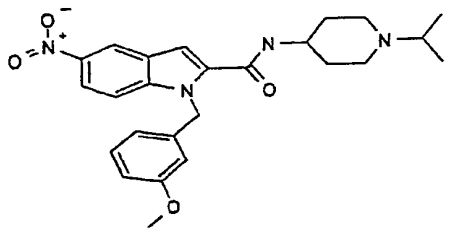
[0173]



[0174] The title compound was prepared analogously to Example 52 with the difference that 5-Benzyloxy-1 H-indole-2-carboxylic acid was used instead of 1H-indole-2-carboxylic acid. MS (ESI+): m/e = 512.

Example 71: 1-(3-Methoxy-benzyl)-5-nitro-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

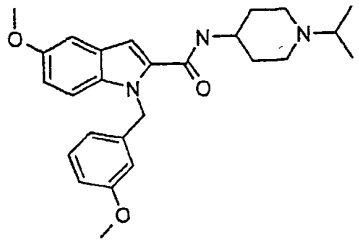
[0175]



[0176] The title compound was prepared analogously to Example 52 with the difference that 5-Nitro-1 H-indole-2-carboxylic acid was used instead of 1 H-indole-2-carboxylic acid.
MS (ESI+): m/e = 451.

Example 72: 5-Methoxy-1-(3-methoxy-benzyl)-1 H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

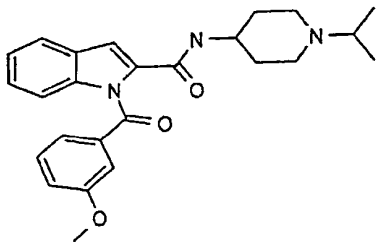
[0177]



[0178] The title compound was prepared analogously to Example 52 with the difference that 5-Methoxy-1 H-indole-2-carboxylic acid was used instead of 1 H-indole-2-carboxylic acid.
MS (ESI+): m/e = 436.

Example 73: 1-(3-Methoxy-benzoyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

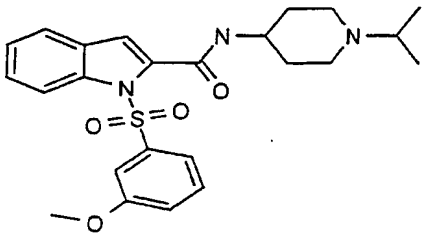
[0179]



[0180] The title compound was prepared analogously to Example 1 with the difference that 3-Methoxy-benzoyl chloride was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. MS (ESI+): m/e = 420.

Example 74: 1-(3-Methoxy-benzenesulfonyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

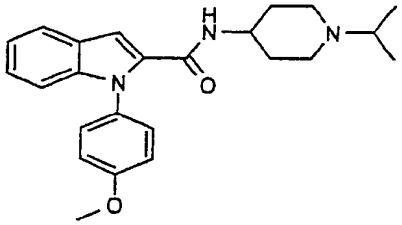
[0181]



[0182] The title compound was prepared analogously to Example 1 with the difference that 3-Methoxy-benzenesulfonyl chloride was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS (ESI+): m/e = 456.

Example 75: 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

[0183]



(i) 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid methyl ester

[0184] To a suspension of 2 g 1H-Indole-2-carboxylic acid methyl ester, 3.2 g 4-Methoxyphenyl boronic acid, 2 g molsieve 4Å, 1.7 ml pyridine, 3 ml NEt_3 in 40 ml DCM 3.9 g $Cu(OAc)_2$ were added. The suspension was stirred for 3 d at RT and for 2 d at 50°C then 3 ml saturated $NaHCO_3$ solution were added and the mixture filtered through a chem elut® cartridge by elution with ethyl acetate. After concentration under reduced pressure and chromatographic purification on silica with ethylacetate/ heptane 4:1 the fractions containing the product were evaporated. Yield: 3 g

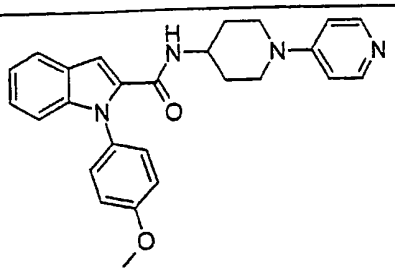
(ii) 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid

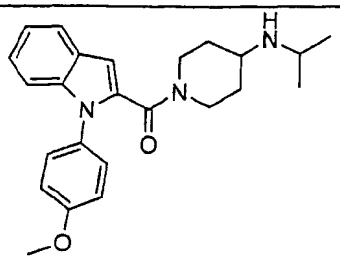
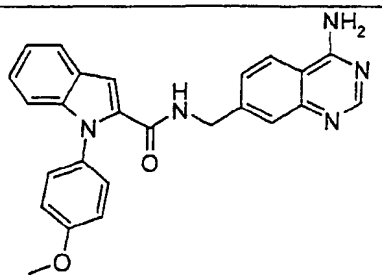
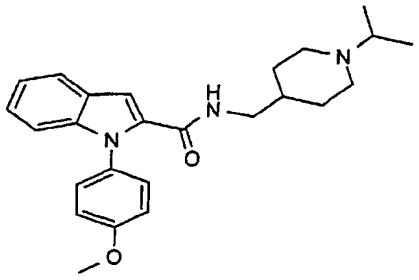
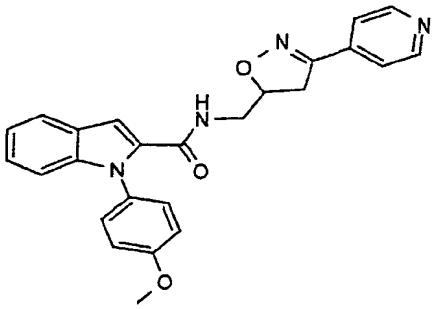
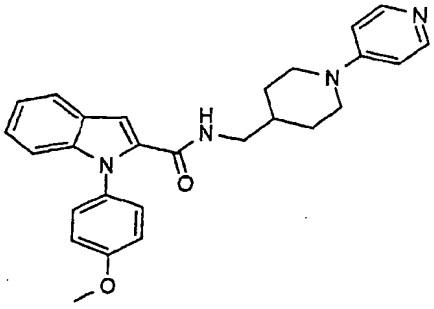
[0185] To a solution of 3 g 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid methyl ester in 50 ml THF 10 ml water and 0.58 g lithium hydroxide monohydrate were added. After stirring for 2 h at 60°C the reaction was cooled to RT: The mixture was acidified with half concentrated hydrochloric acid and the precipitate was collected by filtration and was washed with 10 ml water The product was obtained as a white solid which was dried under reduced pressure. Yield: 520 mg

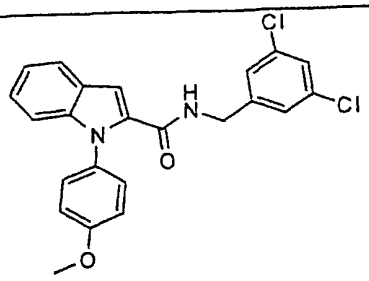
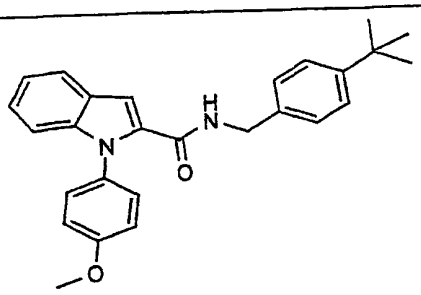
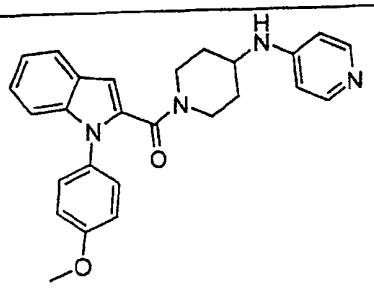
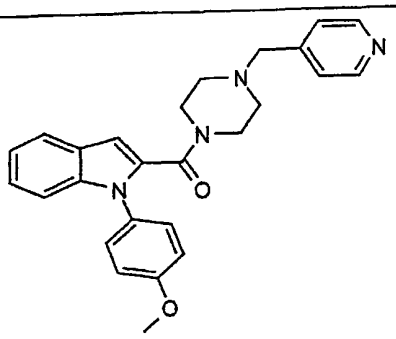
(vi) 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

[0186] To a solution of 36 mg 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid in 1 ml DCM and 0.17 ml NEt_3 34 mg BOP-Cl were added at RT and the mixture was stirred for 30 min. After addition of 57 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride the mixture was stirred over night. Subsequent the solvent was removed of under reduced pressure and the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt. Yield: 14 mg MS (ES^+): m/e = 329.

[0187] According to Example 75 the following compounds were prepared by a similar procedure:

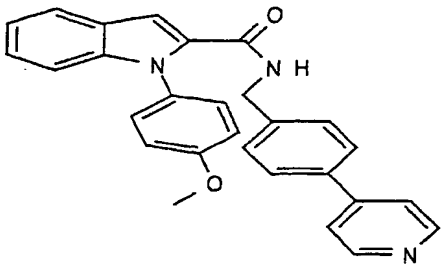
Example	Structure	MS (ESI+)
76		427

77		391
78		424
79		405
80		424
81		441

82		425, chloro pattern
83		413
84		427
85		427

Example 86: 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid 4-pyridin-4-ylbenzylamide

[0188]

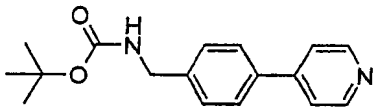


(i) (4-Bromo-benzyl)-carbamic acid tert-butyl ester

[0189] To a solution of 5 g 4-Bromo-benzylamine and 7 ml NEt_3 in 30 ml DCM 5.4 g Boc_2O were added. After stirring over night at RT the reaction mixture was concentrated and the precipitate was collected by filtration. The solid product was dried under reduced pressure and was used in the subsequent reaction without further purification.
Yield: 6.5 g

(ii) (4-Pyridin-4-yl-benzyl)-carbamic acid tert-butyl ester

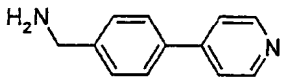
[0190]



[0191] A solution of 500 mg (4-Bromo-benzyl)-carbamic acid tert-butyl ester, 213 mg 4-Pyridyl boronic acid and 500 µl aqueous Na_2CO_3 solution (2M) in 5 ml dimethoxyethane was purged with argon for 15 min. Then 60 mg $Pd(PPh_3)_4$ were added and the mixture was heated to 100°C over night. Finally, 10 ml saturated $NaHCO_3$ solution were added and the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate. After subsequent removal of the solvent under reduced pressure the residue was purified by chromatography on silica with ethylacetate as eluent. The fractions containing the product were evaporated to yield a white solid. Yield: 490 mg

(iii) 4-Pyridin-4-yl-benzylamine

[0192]



[0193] To a solution of 490 mg in 2 ml DCM 3ml TFA were added at RT. After stirring for 12 h the reaction mixture was diluted with 10 ml toluene and was coevaporated to yield a brown foam. The product was obtained as its trifluoro acetate salt. Yield: 330 mg

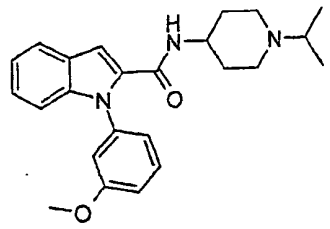
(iv) 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid 4-pyridin-4-yl-benzylamide

[0194] To solution of 50 mg 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid and 100 µl NEt_3 in 2 ml DCM 47 mg BOP-Cl were added at RT. After 1 h 51 mg 4-Pyridin-4-ylbenzylamine were added and the reaction mixture was stirred over night. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H_2O/MeCN gradient with 0.1% TFA). The fractions containing the product were

evaporated and were lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.
Yield: 27 mg MS (ESI+): m/e = 434.

Example 87: 1-(3-Methoxy-phenyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

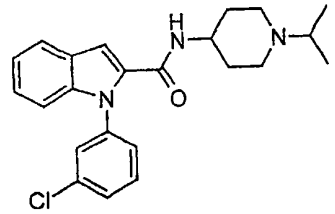
[0195]



[0196] The title compound was prepared analogously to Example 75 with the difference that g 3-Methoxyphenyl boronic acid was used instead of g 4-Methoxyphenyl boronic acid,.
MS (ESI+): m/e = 392.

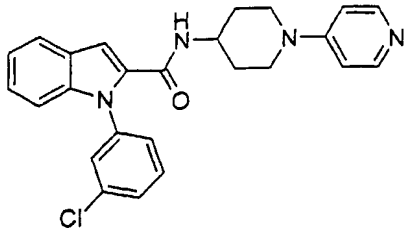
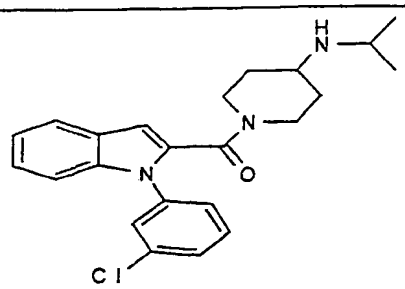
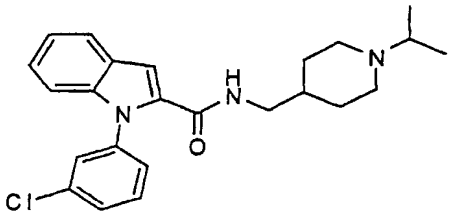
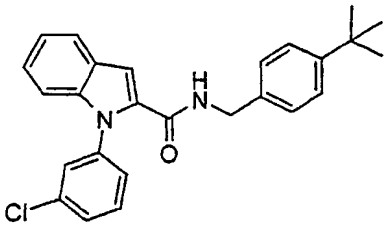
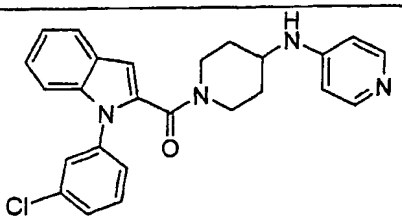
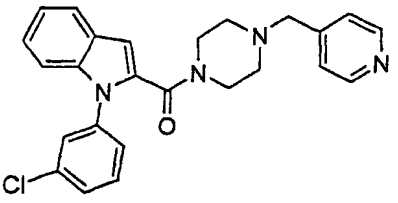
Example 88: 1-(3-Chloro-phenyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

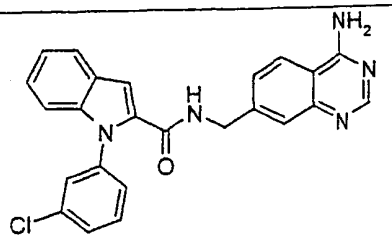
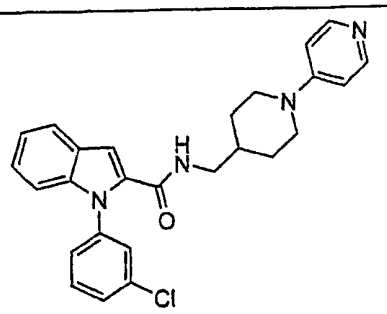
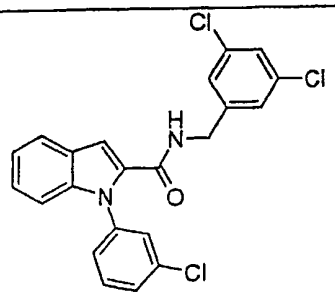
[0197]



[0198] The title compound was prepared analogously to Example 75 with the difference that g 3-Chlorophenyl boronic acid was used instead of g 4-Methoxyphenyl boronic acid,.
MS (ESI+): m/e = 396, chloro pattern.
[0199] According to Example 88 the following compounds were prepared by a similar procedure:

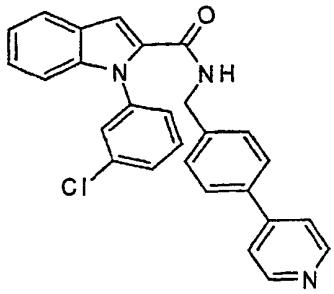
Example	Structure	MS (ESI+)

89		431, chloro pattern
90		396, chloro pattern
91		409, chloro pattern
92		417, chloro pattern
93		431, chloro pattern
94		431, chloro pattern

95		428, chloro pattern
96		445, chloro pattern
97		429, chloro pattern

Example 98: 1-(3-Chloro-phenyl)-1H-indole-2-carboxylic acid 4-pyridin-4-yl-benzylamide

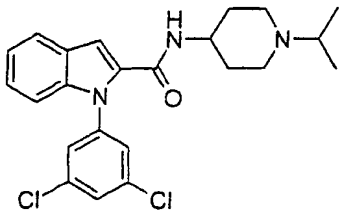
[0200]



[0201] The title compound was prepared analogously to Example 86 with the difference that 1-(3-Chloro-phenyl)-1H-indole-2-carboxylic acid was used instead of 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid.
MS (ESI+): m/e = 438, chloro pattern.

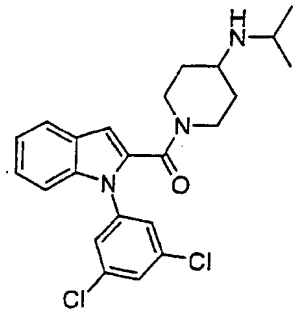
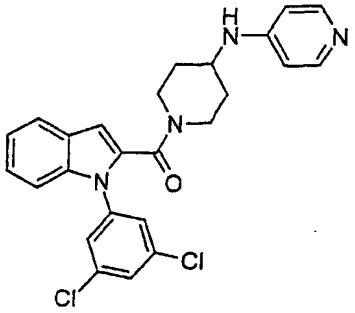
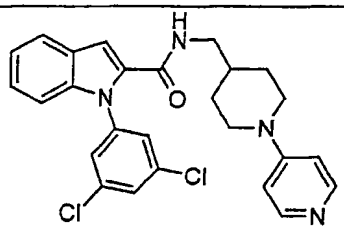
Example 99: 1-(3,5-Dichloro-phenyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

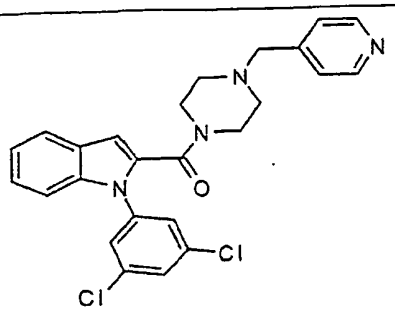
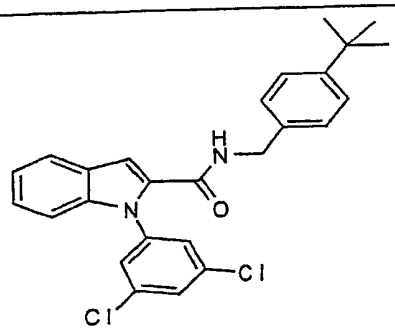
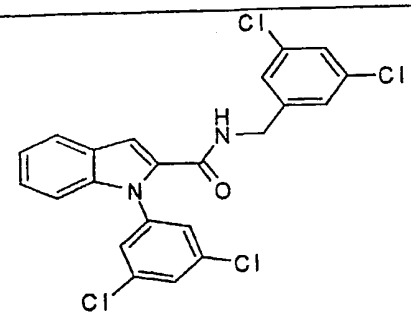
[0202]



[0203] The title compound was prepared analogously to Example 75 with the difference that 3,5-Dichlorophenyl boronic acid was used instead of 4-Methoxyphenyl boronic acid,. MS (ESI+): m/e = 430, chloro pattern.

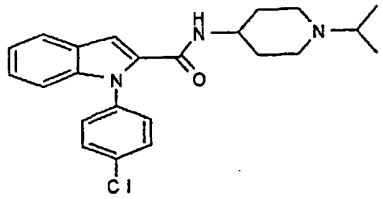
[0204] According to Example 99 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
100		430, chloro pattern
101		465, chloro pattern
102		479, chloro pattern

103		465, chloro pattern
104		451, chloro pattern
105		465, chloro pattern

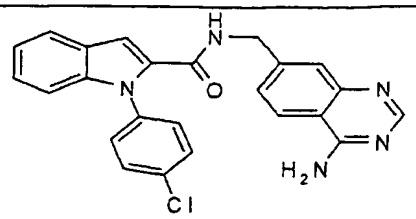
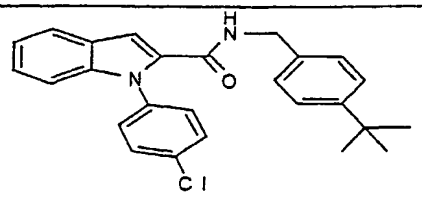
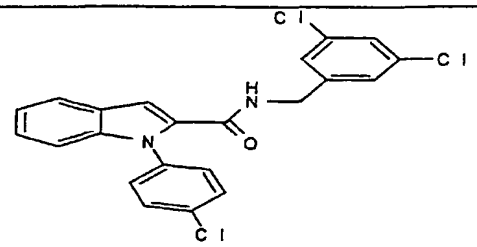
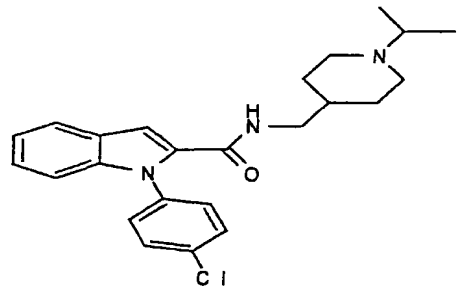
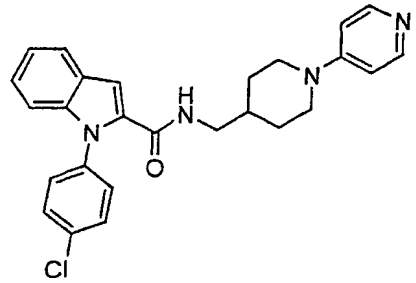
Example 106: 1-(4-Chloro-phenyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

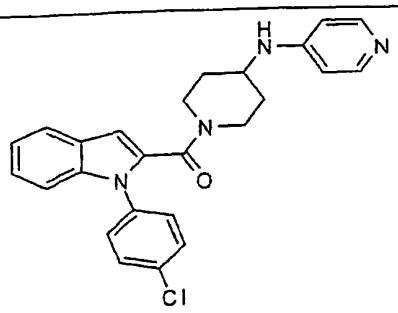
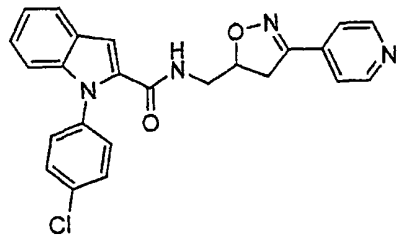
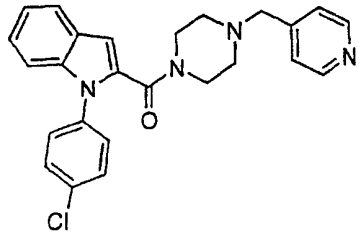
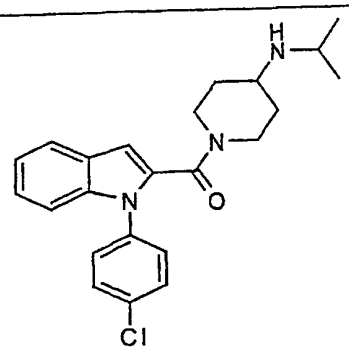
[0205]



[0206] The title compound was prepared analogously to Example 75 with the difference that 4-Chlorophenyl boronic acid was used instead of 4-Methoxyphenyl boronic acid.
MS (ESI+): m/e = 396, chloro pattern.

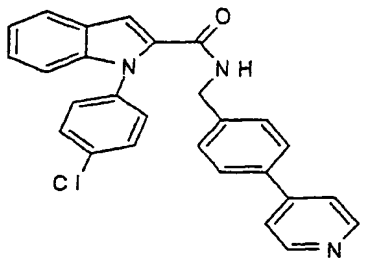
[0207] According to Example 107 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
108		428, chloro pattern
109		415, chloro pattern
110		429, chloro pattern
111		410, chloro pattern
112		445, chloro pattern

113		431, chloro pattern
114		431, chloro pattern
115		431, chloro pattern
116		396, chloro pattern

Example 117: 1-(4-Chloro-phenyl)-1H-indole-2-carboxylic acid 4-pyridin-4-ylbenzylamide

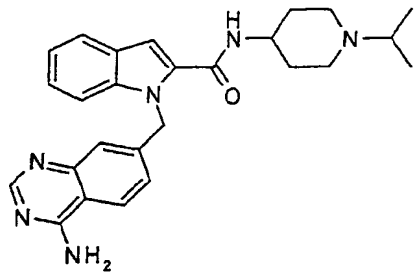
[0208]



[0209] The title compound was prepared analogously to Example 86 with the difference that 1-(4-Chloro-phenyl)-1H-indole-2-carboxylic acid was used instead of 1-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid.
MS (ESI+): m/e 438, chloro pattern.

Example 118: 1-(4-Amino-quinazolin-7-ylmethyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4- yl)-amide

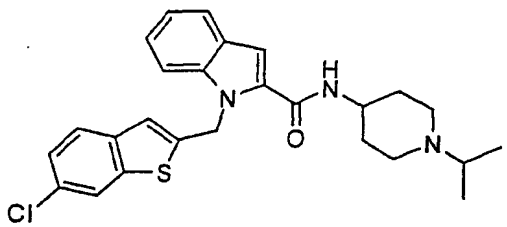
[0210]



[0211] The title compound was prepared analogously to Example 1 with the difference that 7-Bromomethyl-quinazolin-4-ylamine [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B. PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.
MS (ESI+): m/e = 443.

Example 119: 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0212]

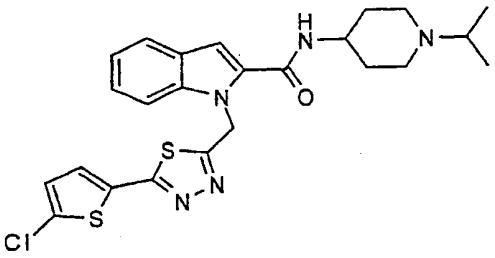


[0213] The title compound was prepared analogously to Example 1 with the difference that 2-Bromomethyl-6-chloro-

benzo[b]thiophene [prepared by adopting a procedure described by Ewing, William R. et al. in ;PCT Int. Appl. (1999), 300 pp. WO 9937304 A1; and Ewing, William R. et al. PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.
MS(ESI+): m/e = 466, chloro pattern.

Example: 120: 1-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

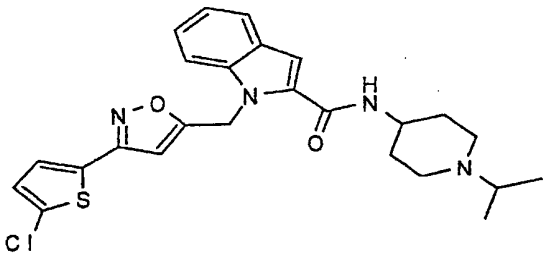
[0214]



[0215] The title compound was prepared analogously to Example 1 with the difference that 2-Bromomethyl-5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazole [prepared by adopting a procedure described by Ewing, William R. et al. PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.
MS(ESI+): m/e = 500, chloro pattern.

Example: 121: 1-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

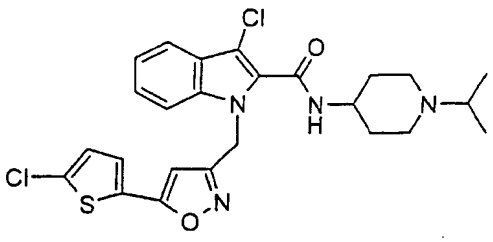
[0216]



[0217] The title compound was prepared analogously to Example 1 with the difference that 5-Bromomethyl-3-(5-chloro-thiophen-2-yl)-isoxazole [Ewing, William R. et al. PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS(ESI+): m/e = 483, chloro pattern.

Example 122: 3-Chloro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

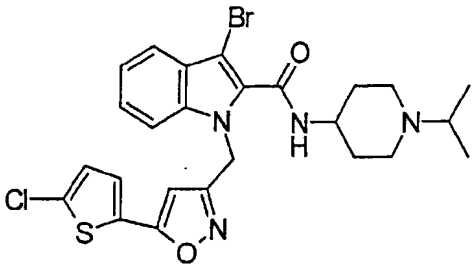
[0218]



[0219] To a solution of 40 mg 1-(5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide in 1 ml DCM 17 mg NCS were added and the mixture was stirred at RT over night. Finally, the reaction mixture was directly purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+ 0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt.
Yield: 15 mg MS (ES+): m/e = 517, chloro pattern

Example 123: 3-Bromo-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

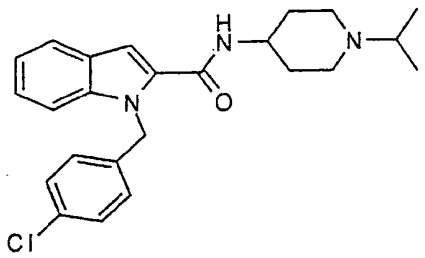
[0220]



[0221] To a solution of 40 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide in 1 ml DCM 22 mg NBS were added and the mixture was stirred at RT over night. Finally, the reaction mixture was directly purified by preparative RP-HPLC eluting with a gradient of 0-100 % acetonitrile in water (+ 0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt.
Yield: 18 mg MS (ES+): m/e = 562, chloro pattern

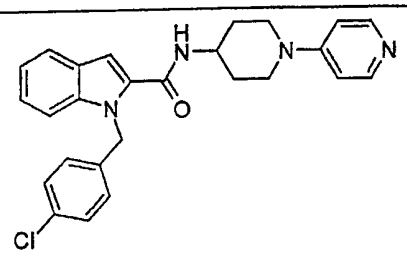
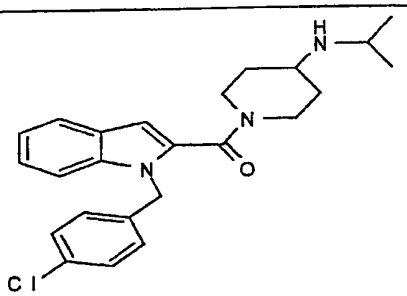
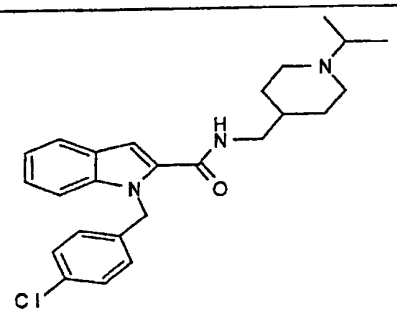
Example 124: 1-(4-Chloro-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

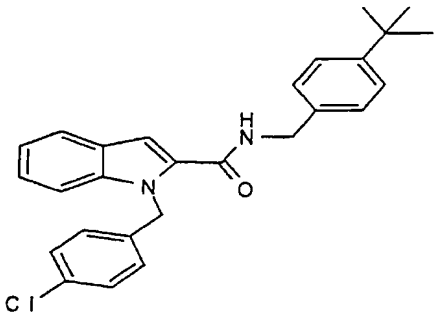
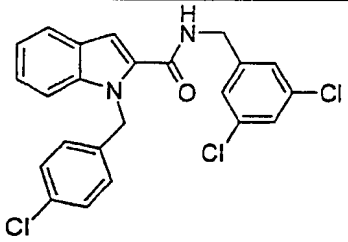
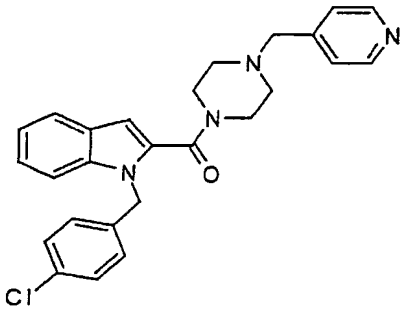
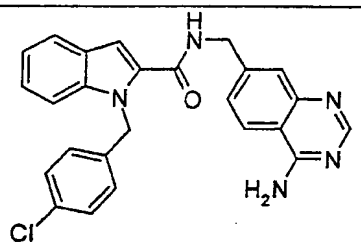
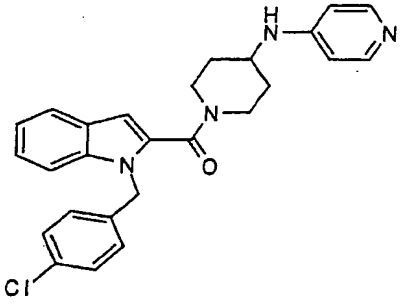
[0222]

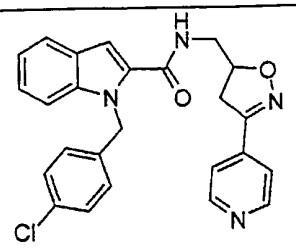
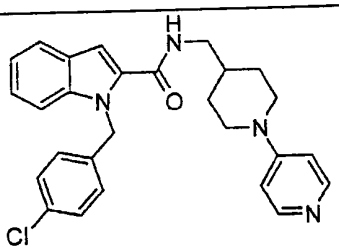


[0223] The title compound was prepared analogously to Example 1 with the difference that 1-Chloromethyl-4-chloro-benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole.
MS (ESI+): m/e = 410, chloro pattern.

[0224] According to Example 124 the following compounds were prepared by a similar procedure:

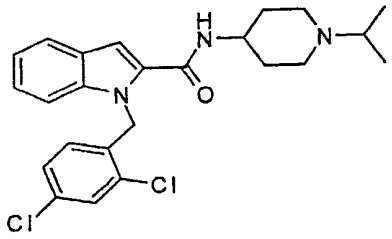
Example	Structure	MS (ESI+)
125		445, chloro pattern
126		409, chloro pattern
127		423, chloro pattern

128		431, chloro pattern
129		443, chloro pattern
130		445, chloro pattern
131		442, chloro pattern
132		445, chloro pattern

133		445, chloro pattern
134		459, chloro pattern

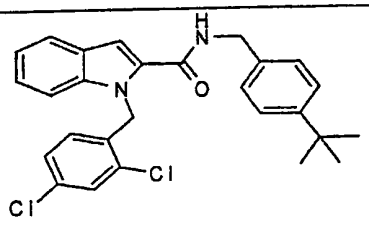
Example 135: 1-(2,4-Dichloro-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

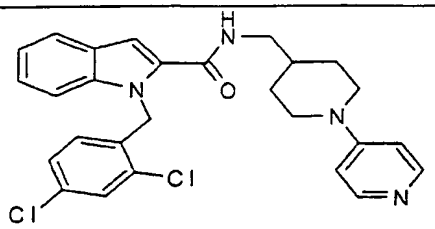
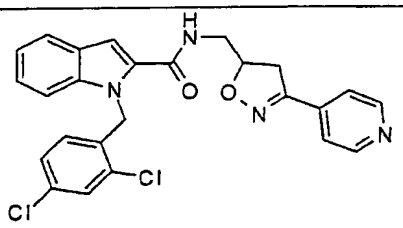
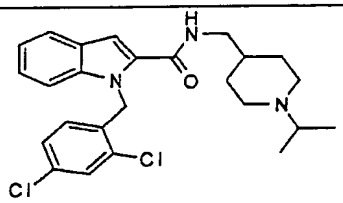
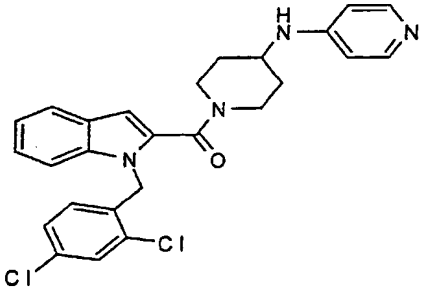
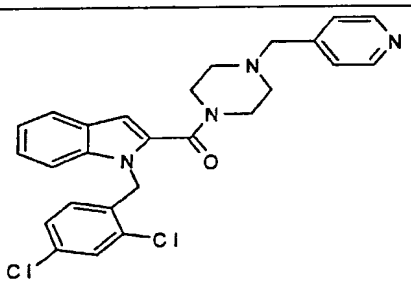
[0225]

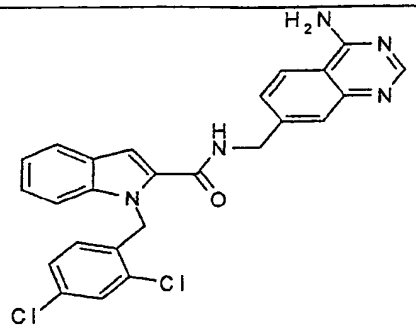
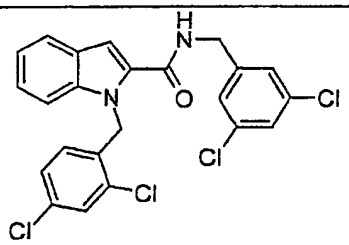


[0226] The title compound was prepared analogously to Example 1 with the difference that 1-Chloromethyl-2,4-dichloro-benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole.
MS (ESI+): m/e = 444, chloro pattern.

[0227] According to Example 135 the following compounds were prepared by a similar procedure:

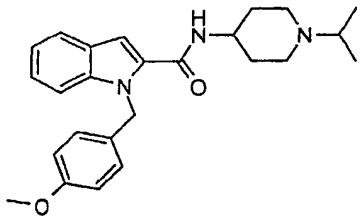
Example	Structure	MS (ESI+)
136		465, chloro pattern

137		493, chloro pattern
138		479, chloro pattern
139		457, chloro pattern
140		479, chloro pattern
141		479, chloro pattern

142		476, chloro pattern
143		478, chloro pattern

Example 144: 1-(4-Methoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

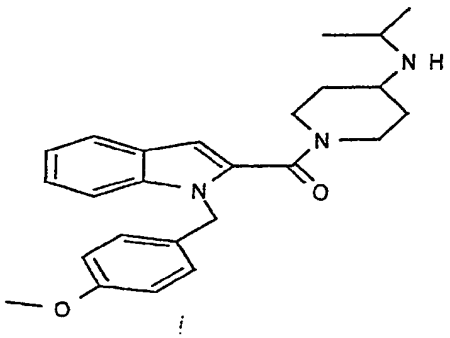
[0228]



[0229] The title compound was prepared analogously to Example 1 with the difference that 1-Chloromethyl-4-methoxy-benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS (ESI+): m/e = 406.

Example 145: (4-Isopropylamino-piperidin-1-yl)-[1-(4-methoxy-benzyl)-1H-indol-2-yl]-methanone

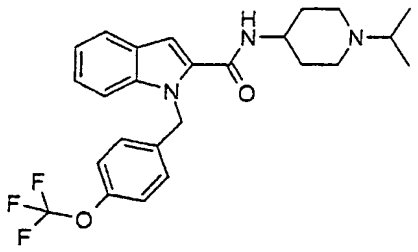
[0230]



[0231] The title compound was prepared analogously to Example 1 with the difference that Isopropyl-piperidin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 406.

Example 146: 1-(4-Trifluoromethoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropylpiperidin-4-yl)-amide

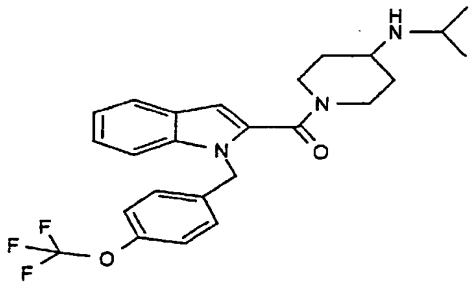
[0232]



[0233] The title compound was prepared analogously to Example 1 with the difference that 1-Bromomethyl-4-trifluoromethoxy-benzene was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. MS (ESI+): m/e = 459.

Example 147: (4-Isopropylamino-piperidin-1-yl)-[1-(4-trifluoromethoxy-benzyl)-1H-indol-2-yl]- methanone

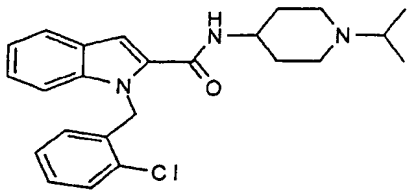
[0234]



[0235] The title compound was prepared analogously to Example 146 with the difference that Isopropyl-piperidin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 459.

Example 148: 1-(2-Chloro-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

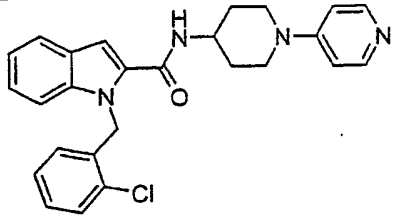
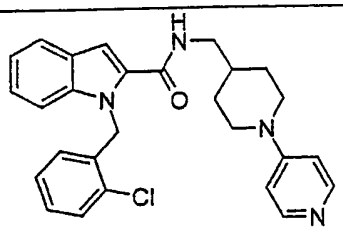
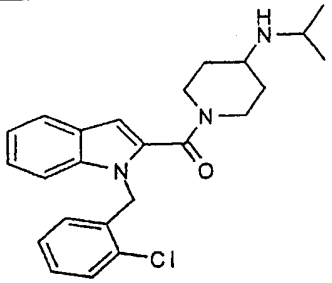
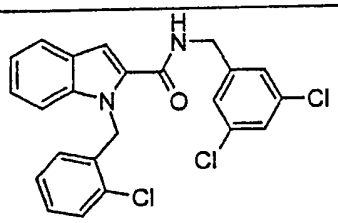
[0236]

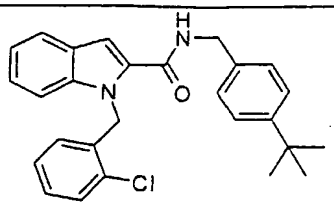
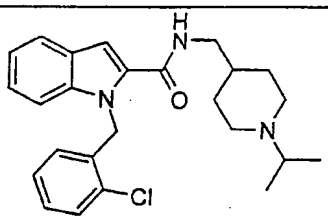
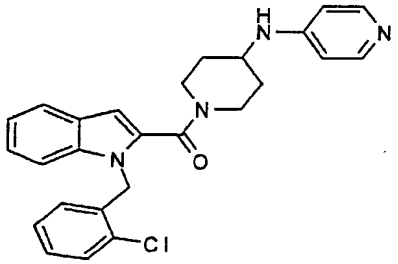
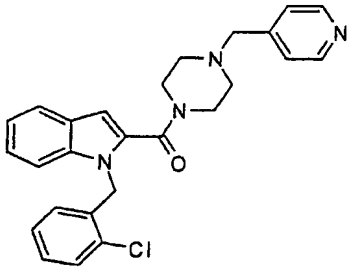


[0237] The title compound was prepared analogously to Example 1 with the difference that 1-Bromomethyl-2-chloro-

benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS (ESI+): m/e = 410, chloro pattern.

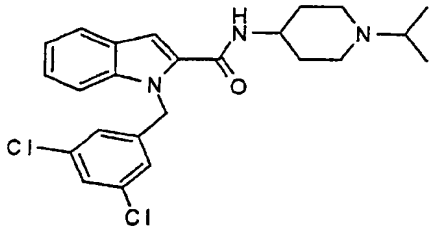
[0238] According to Example 148 the following compounds were prepared by a similar procedure:

Example	Structure	MS (ESI+)
149		410, chloro pattern
150		459, chloro pattern
151		409, chloro pattern
152		443, chloro pattern

153		431, chloro pattern
154		423, chloro pattern
155		445, chloro pattern
156		445, chloro pattern

Example 157: 1-(3,5-Dichloro-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

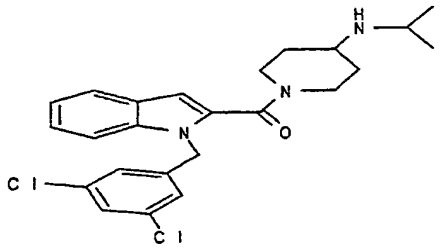
[0239]



[0240] The title compound was prepared analogously to Example 1 with the difference that 1-Chloromethyl-3,5-dichloro-benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS (ESI+): m/e = 444, chloro pattern.

Example 158: [1-(3,5-Dichloro-benzyl)-1H-indol-2-yl]-(4-isopropylamino-piperidin-1-yl)-methanone

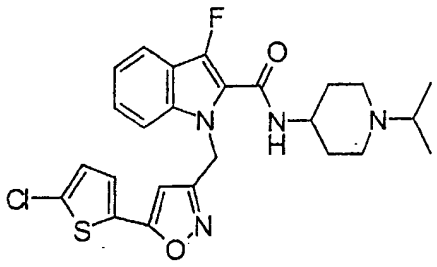
[0241]



[0242] The title compound was prepared analogously to Example 157 with the difference that Isopropyl-piperidin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 443, chloro pattern.

Example 159: 3-Fluoro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

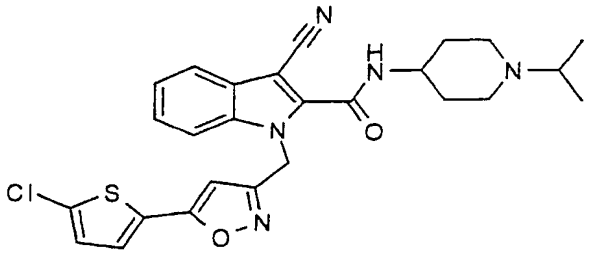
[0243]



[0244] To a solution of 40 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide in 1 ml DCM 22 mg N-Fluoropyridinium triflate were added and the mixture was stirred at RT for 4 days. Finally, the reaction mixture was directly purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01 % trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt.
Yield: 22 mg MS (ES+): m/e = 501, chloro pattern

Example 160: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0245]



(i) 3-Iodo-1H-indole-2-carboxylic acid methyl ester

[0246] To a solution of 2 g 1H-Indole-2-carboxylic acid methyl ester and 2.1 g KOH in 20 ml DMF a solution 2.7 g I_2 in 10 ml DMF were added dropwise at RT. After 30 min the reaction mixture was diluted with a solution of 2.5 g $NaHSO_3$ in 100 ml water. The product was collected as a white precipitate by filtration and was washed with 10 ml water. Yield: 3 g.

(ii) 3-Cyano-1H-indole-2-carboxylic acid methyl ester

[0247] To a solution of 2 g 3-Iodo-1H-indole-2-carboxylic acid methyl ester in 10 ml DMF and 20 ml THF 1.5 g CuCN, 434 mg Et_4NCN, 461 mg DPPF were added and the mixture was purged with argon for 15 min. Then, 254 mg $Pd_2(dba)_3$ were introduced and the reaction was heated to 80 °C for 5 h. Finally, 10 ml saturated $NaHCO_3$ solution were added and the mixture was filtered through a chem elut® cartridge by elution with DCM. After subsequent removal of the solvent under reduced pressure the residue was purified by chromatography on silica with ethylacetate as eluent. The fractions containing the product were evaporated to yield a white solid. Yield: 1.2 g

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid methyl ester

[0248] This compound was prepared using a procedure analogous to that described for the preparation of Example 1 (iv), using 3-Cyano-1H-indole-2-carboxylic acid methyl ester as the starting material.

(iv) 1 -[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid

[0249] This compound was prepared using a procedure analogous to that described for the preparation of Example 1 (v), using 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid methyl ester as the starting material.

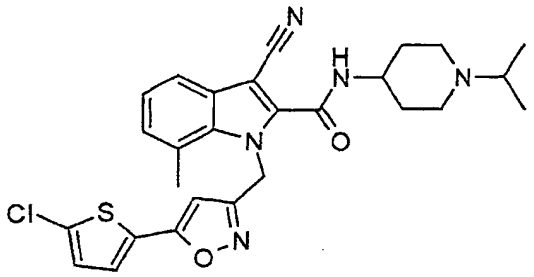
(v) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0250] This compound was prepared using a procedure analogous to that described for the preparation of Example 1 (vi), using 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid as the starting material.

MS (ES^+): m/e = 508, chloro pattern

Example 161: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-7-methyl-1Hindole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

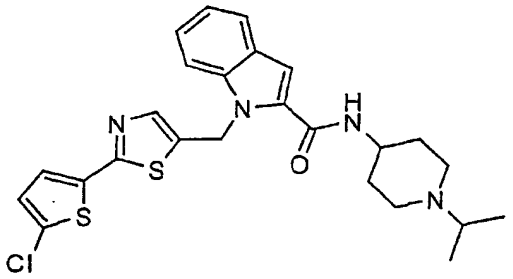
[0251]



[0252] The title compound was prepared analogously to Example 186 with the difference that 7-Methyl-1H-indole-2-carboxylic acid methyl ester was used instead of 1H-Indole-2-carboxylic acid methyl ester. MS (ESI+): m/e = 522, chloro pattern.

Example 162: 1-[2-(5-Chloro-thiophen-2-yl)-thiazol-5-ylmethyl]-1 H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

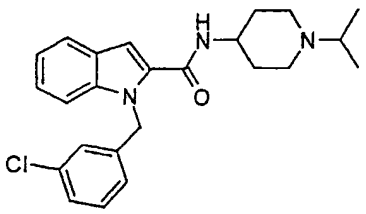
[0253]



[0254] The title compound was prepared analogously to Example 1 with the difference that 5-Bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole [prepared by adopting a procedure described by Ewing, William R. et al.; PCT Int. Appl. (2001), 460 pp. WO 0107436 A2] was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.
MS (ESI+): m/e = 499, chloro pattern.

Example 163: 1-(3-Chloro-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0255]

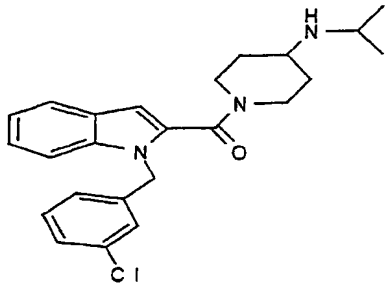


[0256] The title compound was prepared analogously to Example 1 with the difference that 1-Bromomethyl-3-chloro-

benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS (ESI+): m/e = 410, chloro pattern.

Example 164: [1-(3-Chloro-benzyl)-1H-indol-2-yl]-(4-isopropylamino-piperidin-1-yl)-methanone

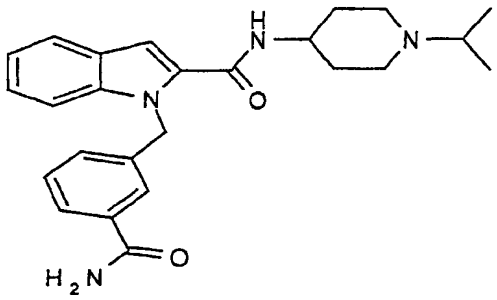
[0257]



[0258] The title compound was prepared analogously to Example 163 with the difference that Isopropyl-piperidin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 409, chloro pattern.

Example 165: 1-(3-Carbamoyl-benzyl)-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

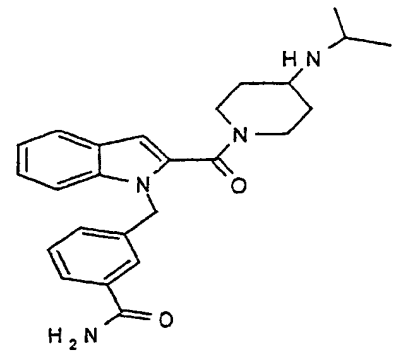
[0259]



[0260] The title compound was prepared analogously to Example 1 with the difference that 3-Bromomethyl-benzamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole. MS (ESI+): m/e = 419.

Example 166: 3-[2-(4-Isopropylamino-piperidine-1-carbonyl)-indol-1-ylmethyl]-benzamide

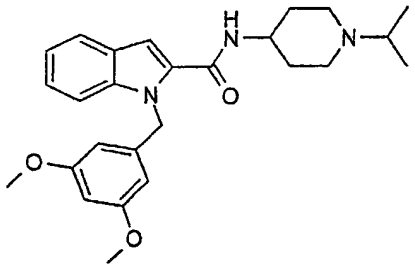
[0261]



[0262] The title compound was prepared analogously to Example 165 with the difference that Isopropyl-piperidin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 419.

Example 167: 1-(3,5-Dimethoxy-benzyl)-1H-indole-2-carboxylic acid (1-isopropylpiperidin-4-yl)-amide

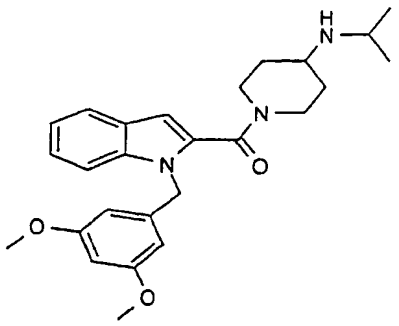
[0263]



[0264] The title compound was prepared analogously to Example 1 with the difference that 1-Chloromethyl-3,5-dimethoxy-benzene was used instead of 3-Bromomethyl-5-(5-chlorothiophen-2-yl)-isoxazole. MS (ESI+): m/e = 435.

Example 168: [1-(3,5-Dimethoxy-benzyl)-1H-indol-2-yl]-(4-isopropylamino-piperidin-1-yl)-methanone

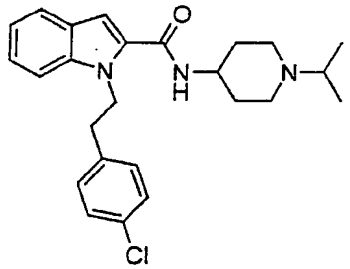
[0265]



[0266] The title compound was prepared analogously to Example 167 with the difference that Isopropyl-piperidin-4-yl-amine was used instead of 1-Isopropyl-piperidin-4-ylamine.
MS (ESI+): m/e = 435.

Example 169: 1-[2-(4-Chloro-phenyl)-ethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide.

[0267]



(i) Toluene-4-sulfonic acid 2-(4-chloro-phenyl)-ethyl ester

[0268] 5 g (31.9mmol) of 2-(4-Chloro-phenyl)-ethanol was dissolved in 100 ml of pyridine and the solution was cooled to 0 °C. 6.09 g (31.9mmol) of para-toluene sulfonyl chloride was added to this solution and the reaction was stirred at 0 °C for 2 h, then at room temperature for 16 h. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed once with saturated aqueous sodium bicarbonate, once with water, and once with saturated aqueous sodium chloride. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The compound was recrystallised from n-heptane/ethyl acetate. Yield 6.23 g. MS (Cl^+): m/e = 311 ($M+H^+$).

(ii) 1-[2-(4-Chloro-phenyl)-ethyl]-1H-indole-2-carboxylic acid ethyl ester

[0269] 0.5g (2.6 mmol) of 1H-Indole-2-carboxylic acid ethyl ester was dissolved in DMF and 116 mg (2.9 mmol) of sodium hydride (60% dispersion in mineral oil) was added. The solution was stirred for 30 min at room temperature, then cooled to -78 °C. A solution of 0.82 g (2.6 mmol) of toluene-4-sulfonic acid 2-(4-chloro-phenyl)-ethyl ester in DMF was added to this cooled solution. The solution was warmed to RT and was stirred for 16 h. The solvent was removed under reduced pressure, the residue was taken-up in ethyl acetate and the solution was washed once with saturated aqueous sodium bicarbonate, once with water, and once with saturated aqueous sodium chloride. The organic phase was dried with magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of n-heptane/ethyl acetate.

Yield 480 mg. MS (Cl^+): m/e = 328 ($M+H^+$).

(iii) 1-[2-(4-Chloro-phenyl)-ethyl]-1H-indole-2-carboxylic acid

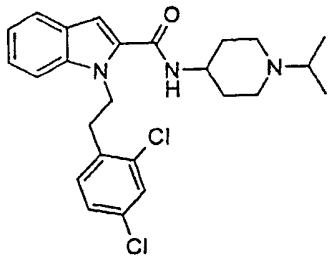
[0270] 480 mg (1.5mmol) of 1-[2-(4-Chloro-phenyl)-ethyl]-1H-indole-2-carboxylic acid ethyl ester was dissolved in 5 ml of dioxan and 5 ml of 2N aqueous sodium hydroxide was added. The reaction was heated to 60 °C for 2 h, then was cooled to 0 °C. The solution was diluted with 10 ml of water and the pH of the solution was adjusted to between 2 and 3 by the addition of concentrated aqueous HCl, whereupon the product precipitates. The product was filtered off and dried under reduced pressure.
Yield 390 mg. MS (Cl^+): m/e = 300 ($M+H^+$).

(iv) 1-[2-(4-Chloro-phenyl)-ethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

[0271] 50mg (0.2mmol) of 1-[2-(4-Chloro-phenyl)-ethyl]-1H-indole-2-carboxylic acid was dissolved in 2 ml of DMF and 54.7 mg (0.2 mmol) of TOTU and 0.21 ml (1.7 mmol) of NEM was added. This solution was stirred at room temperature for 30 min. 35.9 mg (0.2 mmol) of 1-isopropyl-piperidin-4-ylamine dihydrochloride was added and the resulting solution was stirred at room temperature for 16 h. The product was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water(+0.01% trifluoroacetic acid). After lyophilization the product was obtained as its trifluoroacetate salt.
Yield 46.9 mg. MS (TOF-ES^+): m/e = 424 ($M+H^+$).

Example 170: 1-[2-(2,4-Dichloro-phenyl)-ethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0272]



(i) Toluene-4-sulfonic acid 2-(2,4-dichloro-phenyl)-ethyl ester

[0273] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (i), using 2-(2,4-dichloro-phenyl)-ethanol as the starting material. The compound was recrystallised from n-heptane/ethyl acetate.
Yield 7.12 g. MS (Cl^+): m/e = 345 (M^+).

(ii) 1-[2-(2,4-Dichlorophenyl)-ethyl]-1H-indole-2-carboxylic acid ethyl ester

[0274] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (ii), and using toluene-4-sulfonic acid 2-(2,4-dichlorophenyl)-ethyl ester as the starting material.
Yield 91 mg. MS (LC-MS-ES^+): m/e = 362 (M^+).

(iii) 1-[2-(2,4-Dichlorophenyl)-ethyl]-1H-indole-2-carboxylic acid

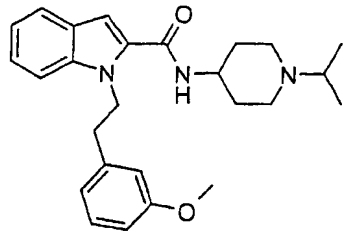
[0275] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (iii), using 1-[2-(2,4-Dichlorophenyl)-ethyl]-1H-indole-2-carboxylic acid ethyl ester as the starting material.
Yield 69 mg. MS (Cl^+): m/e = 334 (M^+).

(iv) 1-[2-(2,4-Dichlorophenyl)-ethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0276] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (iv), using 1-[2-(2,4-Dichlorophenyl)-ethyl]-1H-indole-2-carboxylic acid as the starting material.
Yield 69 mg. MS (Cl+): m/e = 334 (M^+).

Example 171: 1-[2-(3-Methoxy-phenyl)-ethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0277]



(i) Toluene-4-sulfonic acid 2-(3-methoxyphenyl)-ethyl ester

[0278] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (i), using 2-(3-methoxyphenyl)-ethanol as the starting material. The compound was chromatographed on silica gel eluting with n-heptane/ethyl acetate (4/1).
Yield 5.13 g. MS (Cl+): m/e = 306 (M^+).

(ii) 1-[2-(3-Methoxy-phenyl)-ethyl]-1H-indole-2-carboxylic acid ethyl ester

[0279] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (ii), using toluene-4-sulfonic acid 2-(3-methoxyphenyl)-ethyl ester as the starting material.
Yield 554 mg. MS (LC-MS-ES+): m/e = 324 ($M+H^+$).

(iii) 1-[2-(3-Methoxy-phenyl)-ethyl]-1H-indole-2-carboxylic acid

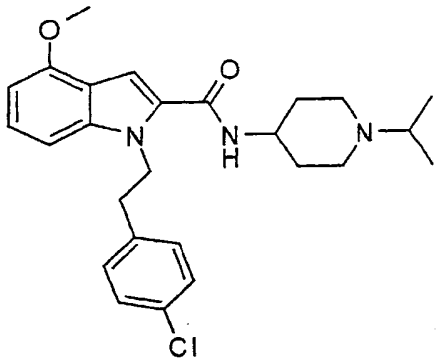
[0280] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (iii), using 1-[2-(3-Methoxy-phenyl)-ethyl]-1H-indole-2-carboxylic acid ethyl ester as the starting material.
Yield 384 mg. MS (Cl+): m/e = 296 ($M+H^+$).

(iv) 1-[2-(3-Methoxy-phenyl)-ethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide

[0281] This compound was prepared using a procedure analogous to that described for the preparation of Example 169 (iv), using 1-[2-(3-Methoxy-phenyl)-ethyl]-1H-indole-2-carboxylic acid as the starting material.
Yield 44 mg. MS (LC-MS-ES+): m/e = 419 (M^+).

Example 172: 1-[2-(4-Chloro-phenyl)-ethyl]-4-methoxy-1H-indole-2-carboxylic acid (1-isopropyl- piperidin-4-yl)-amide

[0282]



[0283] This compound was prepared using a procedure analogous to that described for the preparation of Example 169, using 4-methoxy-1H-indole-2-carboxylic acid methyl ester as the starting material.
Yield 67 mg. MS (ES^+): m/e = 454 (M^+).

Pharmacological testing

[0284] The ability of the compounds of the formula I to inhibit factor Xa or factor VIIa or other enzymes like thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC_{50} value, which was related to the inhibition constant Ki. Purified enzymes were used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis was determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant Ki, the IC_{50} value was corrected for competition with substrate using the formula

$$Ki = IC_{50} / \{1 + (\text{substrate concentration} / Km)\}$$

wherein Km is the Michaelis-Menten constant (Chen and Prusoff, Biochem. Pharmacol. 22 (1973), 3099-3108; I. H. Segal, Enzyme Kinetics, 1975, John Wiley & Sons, New York, 100-125; which were incorporated herein by reference).

a) Factor Xa Assay

[0285] In the assay for determining the inhibition of factor Xa activity TBS-PEG buffer (50 mM Tris-HCl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN_3) was used. The IC_{50} was determined by combining in appropriate wells of a Costar half-area microtiter plate 25 µl human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, Indiana) in TBS-PEG; 40 µl 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N(α)-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin, Ohio) in TBS-PEG.
The assay was performed by pre-incubating the compound of formula I plus enzyme for 10 min. Then the assay was initiated by adding substrate to obtain a final volume of 100 µl. The initial velocity of chromogenic substrate hydrolysis was measured by the change in absorbance at 405 nm using a Bio-tek Instruments kinetic plate reader (Ceres UV900HDi) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The enzyme concentration was 0.5 nM and substrate concentration was 140 µM.

b) Factor VIIa Assay

[0286] The inhibitory activity towards factor VIIa/tissue factor activity was determined using a chromogenic assay essentially as described previously (J. A. Ostrem et al., Biochemistry 37 (1998) 1053-1059 which was incorporated herein by reference). Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge,

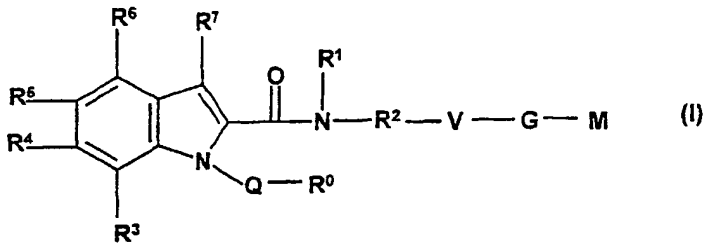
Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A typical assay consisted of 25 µl human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40 µl of inhibitor dilutions in 10% DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM $CaCl_2$, 0.05 % PEG 8000, pH 8.15). Following a 15 minute preincubation period, the assay was initiated by the addition of 35 µl of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500 µM final concentration). The results (inhibition constants Ki (FXa) for inhibition of factor Xa) are shown in Table 1.

Table 1:

Example	Ki(FXa) [µM]	Example	Ki(FXa)[µM]	Example	Ki(FXa) [µM]
1	0,0033	33	0,011	160	0,0001
2	0,020	34	2,997	161	0,0001
3	0,001	35	0,502	162	0,057
4	0,834	36	0,018	163	0,654
5	0,005	37	0,003	165	0,765
6	0,013	38	0,701	169	0,073
7	0,004	39	2,001	170	0,47
8	0,009	41	1,029	172	0,041
9	0,003	43	0,504		
10	0,182	46	0,161		
11	0,0001	47	0,064		
12	0,114	48	0,027		
13	0,00025	50	0,071		
14	1,718	51	0,106		
15	0,0035	52	0,089		
16	0,055	55	1,700		
17	1,966	61	0,475		
18	0,016	66	0,043		
19	0,050	67	0,187		
20	0,007	69	0,159		
21	0,007	70	0,114		
22	0,217	71	0,277		
23	0,003	72	0,167		
24	0,132	119	0,040		
25	0,336	120	0,004		
26	0,0001	121	0,003		
27	0,0002	122	0,002		
28	0,014	123	0,002		
29	0,019	146	0,44		
30	0,025	148	1,930		
31	0,018	157	0,686		
32	0,037	159	0,002		

Claims

1. A compound of the formula I,



(I)

wherein

R^0 is
1. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R^8,
2. a monocyclic or bicyclic 5- to 14-membered heteroaryl out of the group pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, or
3. a monocyclic or bicyclic 5- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8, and which is additionally substituted by a monocyclic or bicyclic 5- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,

R^8 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. $-C(O)-NH_2$,
5. -OH,
6. $-NH_2$,
7. a monocyclic or bicyclic 5- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or $-O-(C_1-C_8)$-alkyl,
8. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue, or
9. $-O-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH_2, -OH or a methoxy residue,

provided that R^8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; $-C(O)-NR^{10}-$, $-NR^{10}-C(O)-$, $-SO_2-$, $-(C_1-C_6)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH; or $-(C_3-C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, $-NH_2$ or -OH;

R^1 is hydrogen atom or $-(C_1-C_4)$-alkyl,

R^2 is a direct bond or $-(C_1-C_4)$-alkylen, or

R^1 and R^2 together with the nitrogen atom and V to which they are bonded form a 5- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -OH, =O, -(C_1-C_4)-alkyl, -(C_1-C_4)-alkoxy, -NO_2, -C(O)-OH, -CN, -NH_2, -C(O)-O-(C_1-C_4)-alkyl, -(C_1-C_8)-alkylsulfonyl, -SO_2, -C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH-[(C_1-C_8)-alkyl]$_2$, -NR^{10}-C(O)-NH-(C_1-C_8)-alkyl, -C(O)-NH_2, -SR^{10}, or -NR^{10}-C(O)-NH-[(C_1-C_8)-alkyl]$_2$,
wherein R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

V is

1. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. a 6- to14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a monocyclic or bicyclic 5- to 14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is

a direct bond, -$(CH_2)_m$-NR^{10}-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-CH(OH)-$(CH_2)_n$-, -$(CH_2)_m$-, -$(CH_2)_m$-O-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-NR^{10}-$(CH_2)_n$-, -(CH_2)-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-C(O)-$(CH_2)_n$-, -$(CH_2)_m$-C(O)-$(CH_2)_n$-, -(CH_2)-S-$(CH_2)_n$-, -$(CH_2)_m$-SO_2-NR^{10}-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-SO_2-$(CH_2)_n$-, -$(CH_2)_m$-NR^{10}-, -$(CH_2)_m$-O-C(O)-NR^{10}-$(CH_2)_n$- or -$(CH_2)_m$-NR^{10}-C(O)-O-$(CH_2)_n$-,

n and m are

are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R^{10} is

hydrogen atom or -(C_1-C_4)-alkyl,

M is

1. a hydrogen atom,
2. -(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -C(O)-$NR^{11}R^{12}$,
4. -$(CH_2)_m$-NR^{10},
5. -(C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
6. -(C_5-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
7. (C_3-C_7)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
8. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, wherein R^{14} is defined above,

R^{11} and R^{12} are

independently of one another identical or different and are

1. hydrogen atom,
2. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
3. -(C_6-C_{14})-aryl-(C_1-C_4)-alkyl-, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13},
4. -(C_6-C_{14})-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
5. -(C_5-C_{14})-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} or
6. -(C_5-C_{14})-heteroaryl-(C_1-C_4)-alkyl-, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R^{13},

R^{11} and R^{12}

together with the nitrogen atom to which they are bonded form a saturated 5- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can

contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{13} is halogen, $-NO_2$, -CN, -OH, $-(C_1-C_8)$-alkyl, $-(C_1-C_8)$-alkyloxy, $-CF_3$, $-C(O)-NH_2$ or $-NH_2$, and

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are hydrogen atom, F, Cl, Br, I, (C_1-C_4)-alkyl, $-CF_3$, phenyl, phenyl-(C_1-C_4)-alkyl-, (C_1-C_4)-alkoxy, wherein alkoxy is unsubstituted or substituted one to three times by halogen, phenyloxy-, phenyl-(C_1-C_4)-alkoxy-, -OH, $-NO_2$, $-NR^{11}R^{12}$, $-NR^{10}-SO_2-R^{10}$, $-S-R^{10}$, $-SO_n-R^{10}$, wherein n is 1 or 2, $-SO_2-NR^{11}R^{12}$, -CN or $-CO-R^{10}$,
wherein R^{10}, R^{11} and R^{12} are as defined above

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2. A compound of the formula I, wherein

R^0 is
1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,
2. a bicyclic 5- to 14-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl,
wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,
and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyridazinyl and pyrazinyl,
wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8
3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl and pyrazinyl,
wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8,
and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^8

R^8 is
1. halogen, such as F, Cl, Br or J,
2. $-C(O)-NH_2$,
3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or
4. $-O-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R^8 is at least one halogen, $-C(O)-NH_2$ or $-O-(C_1-C_8)$-alkyl residue, if R^0 is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -C(O)-; $-SO_2-$ or $-(C_1-C_6)$-alkylen,

R^1 is hydrogen atom or $-(C_1-C_2)$-alkyl,
R^2 is a direct bond or $-(C_1-C_2)$-alkylen, or

R^1 and R^2 together with the nitrogen atom and V to which they are bonded form a 5- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine,

azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine,
wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

R^{14} is halogen, -(C_1-C_4)-alkyl or -NH_2,

V is
1. a 3- to 7-membered cyclic residue out of the group containing compounds which are derived from aziridine, azirine, azetidine, pyrrole, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine,
furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine,
thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,
wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxalinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},

G is a direct bond, -(CH_2)$_m$-, or -(CH_2)$_m$-NR^{10}-,

m is the integers zero, 1, 2, 3 or 4,

R^{10} is hydrogen atom or -(C_1-C_4)-alkyl,

M is
1. a hydrogen atom,
2. -(C_6-C_{14})-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14},
3. -(C_1-C_6)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{14}, or
4. (C_3-C_6)-cycloalkyl,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are hydrogen atom, F, Cl, Br, -(C_1-C_4)-alkyl, -CF_3, -(C_1-C_4)-alkoxy, phenyl-(C_1-C_4)-alkoxy-, -NO_2 or -SO_n-R^{10}, wherein n is 1 or 2, and R^{10} is as defined above,
in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

3. A compound of the formula I as claimed in claim 1 or claim 2, wherein

R^0 is
1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^8, or
2. a monocyclic 5- to 14-membered heteroaryl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heteroaryl is substituted by a residue selected out of the group thienyl, 2-thienyl and 3-thienyl,
wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R^8,

R^8 is F, Cl, Br, methoxyl, -C(O)-NH_2 or -O-CF_3,
Q is a direct bond, -C(O)-; -SO_2-, methylen or ethylene,
R^1 is hydrogen atom,
R^2 is a direct bond or methylen, or

R^1 and R^2 together with the nitrogen atom and V to which they are bonded form a 5- to 7- membered cyclic group out of the group piperidine and piperazine,

R^{14} is halogen, methyl, ethyl or $-NH_2$,

V is
1. a residue out of the group containing compounds which is derived from isoquinol, quinol, quinazoline, piperidine, tetrahydropyran, piperazine and isoxazole,
wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or
2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R^{14}, or

G is a direct bond, $-(CH_2)_m-$, or $-(CH_2)_m-NR^{10}-$,

m is the integers zero, 1 or 2,

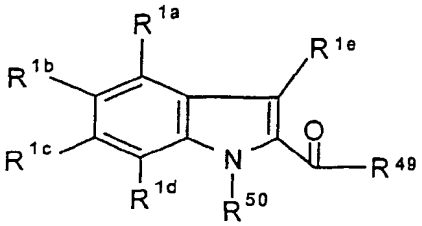
R^{10} is hydrogen atom or $-(C_1-C_4)$-alkyl,

M is a hydrogen atom, (C_2-C_4)-alkyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, pyridinyl or (C_3-C_6)-cylohexyl,

R^3, R^4, R^5, R^6 and R^7 are independent of one another are identical or different and are hydrogen atom, Cl, F, Br, methyl, ethyl, $-O-CF_3$, $-NH-C(O)-C(CH_3)_3$, methoxyl, phenyl, $-O-CH_2$-phenyl, -CN, $-NO_2$ or $-SO_2-CH_3$,
in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4. A compound of the formula I as claimed in one or more of claims 1 to 3, wherein the compound of the formula I is
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-nitro-1H-indole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-nitro-1H-indole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-7-methyl-1H-indole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5,7-dinitro-1H-indole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide,
1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5,7-difluoro-1H-indole-2-carboxylic acid (1- isopropyl-piperidin-4-yl)-amide,
3-chloro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-bromo-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
3-fluoro-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,
1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-cyano-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide or
1 -[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- 3-cyano-7-methyl-1H-indole-2-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

5. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 4, which comprises condensing a compound of the formula 14 with a compound of the formula $HR^{8'}$ to give a compound of the formula 15 and optionally converting the compound of the formula 15 into a compound of the formula I



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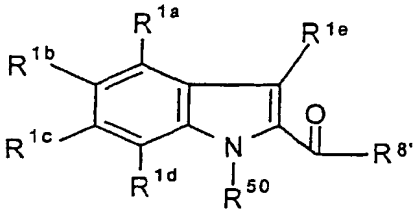

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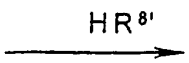

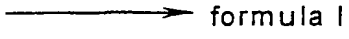

wherein the residue $R^{8'}$ has the donation of-$N(R^1)$-R^2-V-G-M as indicated in claims 1 to 4, but where in $R^{8'}$ functional groups can also be present in the form of groups that are subsequently transformed into the final functional groups present in -$N(R^1)$-R^2-V-G-M, and where the residue R^{50} denotes the group -Q-R^o or can denote a group which is subsequently transformed into the group -Q-R^o, and where the group -C(O)-R^{49} can be a carboxylic acid group or derivatives thereof, and where the groups R^{1e}, R^{1a}, R^{1b}, R^{1c} and R^{1d} in the formulae **14** and **15** have the corresponding definitions of R^7, R^6, R^5, R^4, and R^3 in formula I as defined in claims 1 to 4 or functional groups in them can also be present in protected form or in the form of precursor groups.

6. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in one or more of claims 1 to 4 in all its stereoisomeric forms and mixtures thereof in any ratio and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.

7. The use of a compound of the formula I as claimed in one or more of claims 1 to 4 in all its stereoisomeric forms and mixtures thereof in any ratio and/or their physiologically tolerable salts for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis.

8. The use as claimed in claim 7 for influencing blood coagulation, inflammatory response, fibrinolysis, cardiovascular disorders, thromboembolic diseases, restenoses, abnormal thrombus formation, acute myocardial infarction, unstable angina, acute vessel closure associated with thrombolytic therapy, thromboembolism, percutaneous, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, transluminal coronary angioplasty, transient ischemic attacks, stroke, disseminated systemic intravascular coagulatopathy occurring in vascular systems during septic shock, a risk of pulmonary thromboembolism, certain viral infections or cancer, intravascular coagulatopathy occurring in vascular systems during septic shock, coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder, thromboses like deep vein and proximal vein thrombosis which can occur following surgery.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 12 7809

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Place of search	Date of completion of the search	Examiner
MUNICH	21 February 2002	Herz, C

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X : particularly relevant if taken alone
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